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Reconstructing Skeletal Muscle in Sarcopenia: A Systems-Regeneration Framework Integrating Myogenic Progenitors, Mitochondrial Therapeutics, and Tissue-Specific Peptide Signaling

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Abstract

Sarcopenia is a progressive age-associated disorder characterized by declining skeletal-muscle strength, function, and quantity or quality, with major consequences for mobility, falls, disability, metabolic health, and mortality. Increasing evidence indicates that sarcopenia is not explained by myofiber atrophy alone but reflects deterioration of an integrated regenerative system involving muscle stem-cell competence, mitochondrial quality control, neuromuscular integrity, stromal and immune remodeling, vascular support, and muscle-derived signaling. This review develops a systems-regeneration framework in which three complementary therapeutic domains are considered. We review myogenic precursor/progenitor cells as a candidate substrate for cellular reconstruction as well as mitochondrial-directed therapeutics, including mitochondrial-derived peptides and Mito Organelle biologics, as candidate modulators of metabolic competence. We also discuss tissue-derived Nano Organo Peptides and defined peptide signals as candidate regulators of the regenerative niche.

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Contemporary studies provide strong independent biological support for age-related dysfunction of muscle stem cells and their niche, mitochondrial bioenergetic impairment, and altered myokine signaling in sarcopenia. These observations establish mechanistic rationale for targeting cellular, metabolic, and signaling constraints concurrently but do not establish efficacy of complex organ-derived biologics. Translation requires rigorous product characterization, muscle-specific potency assays, demonstration of target engagement, factorial evaluation of individual and combined components, and validation in aged human muscle models and clinically relevant in vivo systems. The relevant regenerative endpoint is not increased muscle mass alone, but durable restoration of metabolically competent, appropriately innervated skeletal muscle capable of generating meaningful force and improving physical function.

Keywords

Sarcopenia; Skeletal muscle regeneration; Muscle stem cells; Satellite cells; Mitochondrial dysfunction; Mitochondrial-derived peptides; Myokines; Nano Organo Peptides; Mito Organelles; Regenerative medicine.

Introduction

Sarcopenia is an age-associated disorder characterized by progressive deterioration of skeletal-muscle strength, physical function, and muscle quantity or quality [1]. Although diagnostic criteria continue to differ among international consensus groups, contemporary definitions increasingly prioritize muscle strength and functional performance rather than muscle mass alone[2,3]. This distinction is biologically important: aging muscle can lose force-generating capacity disproportionately to changes in bulk tissue, reflecting alterations in muscle composition [4], neuromuscular activation, mitochondrial function, fibrosis, fat infiltration, and cellular regenerative competence. Sarcopenia is consequently associated with falls, fractures, mobility limitation, loss of independence, hospitalization, and mortality and represents a growing clinical burden in aging populations [5].

Current sarcopenia management remains centered on resistance exercise, adequate dietary protein and energy intake, correction of nutritional deficiencies, and treatment of contributing disease [6,7]. These interventions can meaningfully improve muscle strength and function, particularly when exercise and nutritional strategies are combined, but no approved regenerative therapy reliably restores the multicellular architecture and physiological capacity of aged skeletal muscle. The therapeutic gap is therefore not simply failure to increase muscle mass; it is failure to reconstruct the interacting cellular, metabolic, neural, vascular, and signaling systems required for durable contractile function [8].

Skeletal muscle is a contractile, metabolic, endocrine, and regenerative organ whose maintenance depends on coordinated interactions among myogenic progenitors, mature myofibers, stromal and immune populations, vascular networks, and motor neurons. Aging progressively disrupts these relationships through altered muscle stem-cell identity and responsiveness, mitochondrial dysfunction, fibro-adipogenic remodeling, impaired neuromuscular connectivity, and dysregulated peptide signaling. These interdependent changes provide a biological rationale for regenerative approaches addressing more than myofiber hypertrophy alone [9,1011,12,13,14].

This review develops a systems-regeneration framework organized around three complementary

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therapeutic domains: myogenic precursor/progenitor cells as a candidate substrate for cellular reconstruction; mitochondrial-directed therapeutics as potential modulators of metabolic competence; and defined or tissue-derived peptides as candidate regulators of the regenerative microenvironment. The European Wellness (EW) platform is considered as one possible implementation of this architecture, with explicit separation of established muscle biology, experimental therapeutic mechanisms, and product-specific evidence. The scientific value of the model lies in determining whether each domain produces a distinct, measurable biological effect and whether their integration provides additional functional benefit beyond individual components.

Why Skeletal Muscle Regeneration Fails with Aging

Age-related regenerative decline reflects the convergence of impaired muscle stem-cell responsiveness, mitochondrial dysfunction, maladaptive stromal remodeling, and progressive neuromuscular deterioration. These abnormalities are mechanistically interconnected: altered inflammatory and extracellular-matrix signals can compromise myogenic differentiation, mitochondrial impairment can constrain cellular adaptation and contractile performance, and denervation can limit functional recovery despite preservation of muscle tissue [11,12,15,18,19]. Consequently, sarcopenia cannot be understood solely as depletion of muscle mass or loss of anabolic signaling. Its regenerative challenge is the progressive inability to maintain metabolically competent, appropriately innervated, force-generating muscle within a supportive tissue environment [10,15,16,11,12,17,12,18,19]. This distinction is especially important for regenerative interventions because replacement or enlargement of myofibers cannot fully restore muscle function unless adequate neuromuscular connectivity, excitation–contraction coupling, and force transmission are maintained.

Age-associated skeletal-muscle loss reflects an imbalance between muscle protein synthesis and degradation, impaired recovery from catabolic stress, and progressive loss of functional motor units. Reduced responsiveness to dietary amino acids and mechanical loading, commonly termed anabolic resistance, can attenuate activation of protein-synthetic pathways, including PI3K–Akt–mTOR signaling. Concurrently, inflammatory and metabolic stress may increase activity of proteolytic systems involving the ubiquitin–proteasome pathway, autophagy–lysosomal turnover, and the muscle-specific E3 ubiquitin ligases atrogin-1/MAFbx and MuRF1. These processes contribute to reduced myofiber cross-sectional area, particularly when compounded by inactivity, inadequate nutritional intake, or chronic disease. However, sarcopenia also involves deterioration in muscle quality, including intramuscular adipose infiltration, fibrosis, mitochondrial impairment, and motor-unit loss. Consequently, reduced muscle strength may exceed the decline in muscle mass, and interventions that increase myofiber size may not restore proportional improvements in contractile performance.

Myogenic Progenitors as the Cellular Foundation of Muscle Regeneration

Adult skeletal-muscle regeneration is principally mediated by MuSCs, classically defined by their anatomical position beneath the basal lamina and expression of the paired-box transcription factor PAX7 [20]. Following injury or regenerative demand, MuSCs activate myogenic transcriptional programs involving MYF5 and MYOD1, expand as committed progenitors, and subsequently express differentiation regulators such as myogenin before fusing with existing fibers or generating new multinucleated

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myofibers. A subset returns to quiescence, thereby preserving the stem-cell compartment. This hierarchical sequence provides a considerably more rigorous biological benchmark for muscle-directed cellular therapeutics than generic designation as “stem” or “progenitor” cells [11,12]. Notably, regenerative identity cannot be established by anatomical source or expression of an isolated marker. A candidate muscle-directed precursor/progenitor preparation should demonstrate a coherent myogenic phenotype and function, including appropriate PAX7/MYF5/MYOD1/MYOG dynamics, myogenic differentiation, multinucleated myotube formation and fusion, expression of mature contractile proteins, and ultimately contribution to functional muscle tissue. The contribution of muscle stem-cell dysfunction to sarcopenia requires distinction between chronic muscle maintenance and regeneration following injury. PAX7-positive satellite cells are essential for efficient repair of damaged skeletal muscle, but their contribution to the maintenance of uninjured adult myofibers is more context dependent. Aging may impair satellite-cell activation, proliferative expansion, differentiation, fusion, and self-renewal, thereby limiting the capacity to recover from repeated microinjury, disuse, or other catabolic insults. These defects are compounded by age-associated changes in the surrounding niche, including persistent inflammatory signaling, altered extracellular-matrix stiffness, fibro-adipogenic progenitor dysfunction, and diminished vascular and neural support. Thus, restoring regenerative capacity requires more than expanding the number of progenitor cells; it requires preservation of myogenic identity, productive fusion with existing or newly formed myofibers, maintenance of the stem-cell reserve, and integration into a functional muscle environment.

Where cell administration is proposed, proliferative control, genomic stability, biodistribution, persistence, and inappropriate lineage differentiation are additional requirements. These criteria distinguish bona fide myogenic reconstruction from nonspecific trophic or paracrine effects. This distinction becomes especially important in aging [21]. Age-associated changes in myogenic transcriptional regulation and niche responsiveness further constrain regenerative competence. Accordingly, a candidate muscle-directed progenitor preparation must demonstrate functional myogenic differentiation and, where direct cellular reconstruction is proposed, contribution to contractile tissue. Paracrine or immunomodulatory effects should be evaluated as distinct mechanisms rather than interpreted as evidence of myofiber replacement [16,22,11,16]. For administered precursor/progenitor products, demonstration of myogenic lineage identity should be distinguished from evidence of functional engraftment. Relevant experiments include expression of PAX7, MYOD1, MYOG, and mature contractile proteins; myotube formation and fusion; persistence of donor-derived cells; and contribution to contractile force. If a preparation lacks viable myogenic progenitors, its potential activity should instead be evaluated as a paracrine, immunomodulatory, or trophic mechanism rather than direct cellular replacement.

The Regenerative Niche and Fibro-Adipogenic Remodeling

Muscle regeneration depends on coordinated interactions among MuSCs, fibro-adipogenic progenitors (FAPs), immune and vascular cells, and extracellular-matrix components [12]. FAPs illustrate the context-dependent nature of this signaling: transient activation supports matrix remodeling and myogenesis, whereas persistent inflammatory and stromal dysregulation can favor fibrosis and intramuscular adipose accumulation [18]. Consequently, stimulation of myogenic proliferation may provide limited benefit when

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the surrounding niche remains structurally or metabolically unfavorable. Effective regeneration requires both competent myogenic cells and an environment capable of supporting their differentiation and functional integration [18].

Mitochondrial Competence as a Metabolic Requirement for Muscle Regeneration

Skeletal muscle is exceptionally dependent on mitochondrial function because sustained contraction and adaptation require continuous coordination of ATP production, substrate oxidation, redox signaling, calcium homeostasis, organelle turnover, and metabolic communication. Mitochondria are therefore not simply energy generators; mitochondrial quality control influences cell survival, differentiation, inflammatory signaling, and adaptation to physiological stress. Quality control encompasses coordinated mitochondrial biogenesis, fusion and fission, selective removal of damaged mitochondria through mitophagy, and replacement of dysfunctional organelles [23]. These processes become increasingly disturbed in sarcopenia. Mitochondrial bioenergetics are reduced in older muscle and correlate with clinically meaningful measures including aerobic capacity, muscle strength, and physical performance. Altered autophagy and mitophagy signatures have also been associated with reduced muscle volume and performance, supporting the proposition that loss of mitochondrial quality control contributes directly to the sarcopenic phenotype rather than simply accompanying it [15]. This evidence establishes a strong rationale for mitochondrial-directed therapy but requires careful distinction among fundamentally different interventions. Strategies that stimulate endogenous mitochondrial biogenesis or mitophagy, defined mitochondrial-derived peptides, pharmacologic mitochondrial modulators, extracellular mitochondrial transfer, and administration of isolated mitochondrial preparations are biologically distinct modalities. Evidence supporting one cannot be used as evidence of efficacy for another. Nevertheless, direct mitochondrial supplementation has begun to generate proof-of-concept evidence relevant to muscle. In aged mice, intramuscular transplantation of isolated mitochondria increased cytochrome-c oxidase and citrate-synthase activity, ATP concentrations, and mitochondrial protein markers and was associated with improved exercise tolerance. This provides experimental evidence that exogenous mitochondrial delivery can modify aged skeletal-muscle bioenergetics, but it remains an early preclinical observation and does not establish efficacy in human sarcopenia [24]. More recent work using plasma-derived mitochondria demonstrated preserved structural integrity and respiratory activity of the preparation, increased ATP production and mitochondrial function in an in vitro muscle-atrophy model, and improved muscle morphology following intramuscular administration in a rat model of postsurgical paraspinal muscle atrophy. Again, these findings provide proof of biological feasibility rather than evidence for treatment of age-related sarcopenia [25]. These findings establish preclinical feasibility for mitochondrial delivery but cannot be extrapolated directly to complex Mito Organelle (MO) preparations. The composition of an MO product, including the relative presence of intact respiration-competent mitochondria, membrane fragments, proteins, peptides, nucleic acids, and metabolites, determines its plausible mechanism and appropriate potency assays. For muscle-directed applications, mitochondrial target engagement should be demonstrated through measures of respiration, ATP production, redox homeostasis, and mitochondrial quality control, with uptake and intracellular persistence assessed when intact organelle transfer is proposed. These measures must subsequently be linked to myotube integrity, myogenic differentiation, protein turnover, and contractile function.

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Mitochondrial-derived peptides as a mechanistic bridge

Mitochondrial-derived peptides (MDPs) provide an important conceptual bridge between mitochondrial biology and peptide-based therapeutics. Unlike complex mitochondrial preparations, MDPs such as MOTS-c and Humanin are molecularly defined signals encoded within mitochondrial sequences and can therefore be evaluated using conventional pharmacologic criteria including identity, dose, receptor or molecular target, exposure, pathway engagement, and dose-response. Recent mechanistic evidence is particularly relevant to skeletal muscle. MOTS-c has been shown to bind directly to and activate casein kinase 2 (CK2). In mice, MOTS-c administration attenuated skeletal-muscle atrophy and enhanced muscle glucose uptake; suppression of CK2 activity attenuated these effects. A naturally occurring K14Q MOTS-c variant exhibited reduced CK2 binding and activity, and male carriers showed an age- and physical-activity-dependent increase in sarcopenia risk. These findings provide unusually strong mechanistic evidence linking a defined mitochondrial microprotein, a molecular target, muscle biology, and a human genetic variant [26].

In a separate mouse immobilization model, MOTS-c attenuated skeletal-muscle loss and lipid infiltration, accompanied by changes in AKT–FOXO signaling and inflammatory mediators [26]. These findings complement, but are mechanistically distinct from, evidence implicating direct CK2 activation in MOTS-c-mediated regulation of muscle function [26]. Most recently, direct studies in primary human skeletal-muscle myotubes demonstrated that both MOTS-c and the Humanin analogue S14G-Humanin attenuated dexamethasone-induced atrophy. MOTS-c preserved myotube area and fusion and was associated with enhanced Akt phosphorylation and suppression of MuRF1 and STAT3 responses, whereas Humanin preserved myotube area and attenuated STAT3 activation. These findings substantially strengthen the translational biological rationale for defined MDPs while remaining preclinical and model-specific [27]. This evidence should not, however, be extrapolated directly to complex mitochondrial extracts. Defined MOTS-c or Humanin treatment establishes that mitochondrial genomes encode bioactive peptides capable of regulating muscle biology; it does not demonstrate that an MO preparation contains those peptides at biologically effective concentrations, delivers them to muscle, or acts through the same mechanisms. For MO development, those propositions require direct compositional and target-engagement studies.

European Wellness Mito Organelle (MO) preparations represent a separate investigational modality whose proposed contribution to muscle regeneration is restoration or support of mitochondrial metabolic competence. Their mechanism must be defined according to the actual composition of the administered preparation. If intact, respiration-competent mitochondria are present, relevant mechanisms may include cellular uptake and modification of mitochondrial bioenergetics. If the preparation primarily contains mitochondrial fragments, proteins, lipids, peptides, or metabolites, its biological activity may instead reflect signaling or metabolic effects independent of intact organelle transfer. These possibilities require distinct analytical and functional assays. Accordingly, evidence that defined mitochondrial-derived peptides such as MOTS-c or Humanin attenuate experimental muscle atrophy should be presented as mechanistic precedent, not direct evidence of MO product efficacy.

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Peptide-mediated regulation of muscle homeostasis and wasting

Peptide signaling regulates skeletal-muscle protein turnover, metabolic adaptation, inflammatory responses, and myogenic differentiation. A 2025 scoping review identified 87 peptides across 126 studies addressing muscle mass, strength, physical performance, or sarcopenia, with major signaling networks involving PI3K/Akt/mTOR, activin receptor/SMAD, IKK/NF-κB, and AMPK/PGC-1α [28]. Although this literature establishes broad mechanistic relevance, substantial heterogeneity in experimental design, peptide measurement, and clinical validation limits extrapolation to therapeutic efficacy. translational maturity. Peptide-mediated regulation of skeletal-muscle mass can be organized into three partially overlapping functional domains. First, anabolic signals, including insulin-like growth factor-1 (IGF-1), promote protein synthesis and myogenic responses through pathways involving PI3K–Akt–mTOR signaling. Second, negative regulators of muscle growth, particularly myostatin/GDF8 and activin-family ligands, signal through activin receptors and SMAD2/3 to constrain muscle growth and influence protein turnover. Third, metabolic and stress-responsive peptides, including selected myokines and mitochondrial-derived peptides, may modify substrate utilization, inflammatory signaling, mitochondrial function, and susceptibility to atrophy. These pathways differ substantially in their effects on muscle quantity, regenerative-cell behavior, and contractile performance. Accordingly, evidence of anabolic signaling or reduced expression of atrophy-associated proteins should be interpreted as pathway engagement rather than definitive evidence of functional muscle regeneration.

The myostatin/activin axis provides perhaps the clearest example of peptide-mediated control of muscle mass. Myostatin, or growth differentiation factor 8, signals through activin type II receptors and downstream SMAD pathways to constrain skeletal-muscle growth. Recent randomized human Phase I evidence further supports activin A as an additional negative regulator: combined blockade of GDF8 and activin A produced greater muscle growth than GDF8 inhibition alone and approached the effect of broader activin-receptor blockade. These findings demonstrate that peptide-regulated muscle mass is biologically manipulable in humans, while also illustrating why increases in muscle quantity cannot automatically be equated with restoration of strength or physical function [29]. This distinction is essential. A peptide may alter hypertrophy, proteolysis, mitochondrial metabolism, inflammation, or progenitor-cell behavior without reconstructing the integrated tissue required for functional recovery. Peptide potency should therefore be defined according to the proposed mechanism rather than by generalized proliferative or “regenerative” activity. The distinction between hypertrophy and functional recovery is particularly relevant to myostatin-directed therapies. Pharmacological inhibition of negative muscle-growth regulators can increase lean mass or muscle volume, but functional outcomes depend on additional determinants, including muscle architecture, neural activation, mitochondrial capacity, and physical conditioning. Consequently, increases in muscle quantity should be accompanied by assessments of strength, power, and physical performance before a clinically meaningful benefit can be established.

Nano organo peptides as a tissue-contextual signaling hypothesis

Nano Organo Peptides (NOPs) represent a candidate approach to modulating tissue-contextual signaling through complex tissue-derived peptide preparations. Although established peptide biology provides a mechanistic rationale for investigation, the composition, target engagement, and muscle-specific activity of individual NOP preparations must be demonstrated directly. Candidate effects include regulation of

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myogenic differentiation, anabolic and catabolic signaling, mitochondrial stress responses, inflammatory pathways, and fibro-adipogenic remodeling. These mechanisms should be evaluated separately, with tissue selectivity assessed through direct comparison against appropriately characterized preparations derived from other organs. Tissue origin alone does not establish pharmacological specificity. Within the European Wellness (EW) platform, muscle-directed NOPs are proposed as tissue-derived preparations intended to influence signaling processes relevant to skeletal-muscle maintenance and regeneration. Their potential therapeutic rationale is supported indirectly by established evidence that defined peptides regulate myogenic differentiation, protein turnover, metabolic adaptation, and interactions between muscle cells and their supporting microenvironment. However, the biological properties of endogenous peptides cannot be assigned automatically to a complex NOP preparation. Product-specific evidence is required to establish peptide composition, relative abundance, stability, biologically effective exposure, and reproducible activity in skeletal-muscle models. In particular, the tissue of origin should be considered a starting hypothesis for biological specificity rather than evidence that the preparation selectively targets skeletal muscle.

Neuromuscular integrity as a required component of functional regeneration

Neuromuscular integrity represents an essential functional constraint on skeletal-muscle regeneration. Age-related denervation, impaired reinnervation, motor-unit remodeling, and neuromuscular-junction deterioration contribute to weakness independently of muscle quantity [19]. Consequently, increased myofiber size or improved mitochondrial activity cannot alone establish functional regeneration. Where feasible, preclinical studies should incorporate neuromuscular-junction integrity, motor-unit function, and direct measures of contractile force to determine whether structural improvements translate into physiologically meaningful muscle performance [19].

From biological activity to clinically meaningful muscle regeneration

The evidentiary standard for regenerative therapeutics in sarcopenia should reflect the multidimensional nature of the disease. Contemporary regulatory discussions emphasize that muscle quantity alone is insufficient and identify validated physical-performance outcomes, including SPPB, habitual gait speed, stair-climb performance, and the six-minute walk test, as important clinical-trial endpoints [30]. This is consistent with the broader biological framework developed here: structural change is meaningful only when it translates into improved muscle performance. Any novel regenerative strategy must also be evaluated against an active therapeutic landscape. A 2025 network meta-analysis encompassing 96 studies and 7,596 participants found high-certainty evidence supporting combined resistance/balance training and protein-based nutritional supplementation for improving strength, muscle mass, and physical function in sarcopenia [31]. Novel biologics should therefore be conceptualized as potential adjuncts for patients with persistent regenerative deficits, impaired responsiveness, or specific mechanistic abnormalities rather than substitutes for evidence-based exercise and nutritional therapy. For candidate PSC, MO, and NOP interventions, a translational hierarchy can therefore be defined: product identity and composition; molecular target engagement; cell- and tissue-specific biological activity; structural muscle regeneration; restoration of contractile function; and clinically meaningful improvement in strength and physical performance. Advancement across these levels should require evidence at the preceding level rather than inference from biological plausibility.

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European wellness (EW) as a candidate platform for muscle regeneration

The EW platform provides a candidate implementation of the systems-regeneration framework through muscle-directed precursor/progenitor preparations, MO biologics, and NOPs. These modalities are proposed to address complementary constraints on muscle regeneration: cellular reconstruction, metabolic competence, and tissue-contextual signaling. Their integration is biologically plausible, but neither individual therapeutic efficacy nor superiority of combined administration has been established in sarcopenia. Existing EW publications provide a preliminary analytical and conceptual foundation for evaluating these modalities. Published work describing mass-spectrometric analysis of NOP preparations addresses aspects of molecular characterization and stability, whereas reports concerning MO biologics and integrated peptide–mitochondrial approaches describe proposed regenerative applications. These publications do not establish muscle-specific target engagement, restoration of myogenic function, or clinical efficacy in sarcopenia. Their principal relevance is therefore to product characterization and hypothesis development rather than confirmation of therapeutic benefit. For EW PSC approaches, the proposed regenerative mechanism must be distinguished according to whether the administered product contains viable lineage-competent cells, nonmyogenic stromal populations, or cell-free derivatives. Viable myogenic cells could theoretically contribute to tissue reconstruction through engraftment and differentiation, whereas nonmyogenic or cell-free preparations would require demonstration of indirect effects on endogenous muscle cells or their microenvironment. Product characterization should therefore precede claims of myofiber replacement, satellite-cell replenishment, or enhanced muscle regeneration. In the absence of direct lineage-tracing or functional engraftment evidence, these mechanisms remain investigational hypotheses.

The translational rationale for combining PSC, MO, and NOP approaches rests on their proposed ability to address different components of age-associated muscle deterioration. PSC-directed interventions would primarily target impaired cellular regeneration; MO-directed interventions would address mitochondrial metabolic competence; and NOP-directed interventions would investigate peptide-mediated regulation of myogenic, anabolic, or niche-associated signaling. These mechanisms are potentially complementary but are not necessarily synergistic. Demonstrating complementarity requires evidence that each preparation engages a distinct biological target and that combined treatment produces additional functional benefit beyond the effects of individual components. A rigorous evaluation should therefore incorporate factorial experimental designs and distinguish improvements in muscle-cell survival, myotube size, mitochondrial respiration, and myogenic differentiation from improvements in force generation and physical performance.

Sarcopenia-related defect	Candidate EW modality	Proposed mechanism requiring validation	Priority experimental endpoint
Impaired muscle repair and progenitor dysfunction	PSC	Myogenic differentiation, engraftment, or modulation of endogenous progenitors	PAX7/MYOD1/MYOG, fusion index, donor-cell contribution
Reduced mitochondrial bioenergetics	MO	Restoration of mitochondrial function or metabolic signaling	Respiratory capacity, ATP, membrane potential, mitochondrial integrity
Anabolic resistance and proteolysis	NOP	Modulation of anabolic/catabolic signaling	Akt/mTOR, SMAD2/3, MuRF1, atrogin-1, protein turnover
Impaired myotube	NOP ± MO	Improved cellular resilience during	Myotube area, myosin heavy chain,

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maintenance		catabolic stress	viability, contractile force
Multicomponent regenerative dysfunction	PSC + MO + NOP	Complementary cellular, metabolic, and signaling effects	Factorial comparison, muscle force, functional recovery

Table 1: Mechanisms of Age-Associated Skeletal-Muscle Loss and the Experimental Rationale for Candidate European Wellness Interventions.

Translational development and clinical evaluation

The translational development of this platform should begin with rigorous definition of each preparation. Muscle-directed cellular products require confirmation of lineage identity, viability, differentiation potential, and functional myogenic competence. MO preparations require compositional characterization and mechanism-appropriate assessment of mitochondrial or molecular activity. NOP preparations require quantitative peptide profiling, identification of candidate active constituents, batch reproducibility, and evidence of tissue-selective biological activity. Mechanistic evaluation should subsequently determine whether the individual preparations influence distinct but complementary regenerative processes. Human myogenic cultures, engineered muscle tissues, and multicellular niche models provide opportunities to assess myogenic differentiation, mitochondrial function, protein turnover, inflammatory and stromal responses, and contractile performance. Factorial studies examining individual, pairwise, and combined interventions should distinguish independent effects from additive or synergistic interactions. Greater activity of a combination should not be assumed from its broader biological composition. The scientific value of the EW platform ultimately depends on whether reproducibly characterized preparations produce distinct, measurable biological effects and whether their integration improves muscle-specific functional outcomes beyond those achieved by individual components. This approach positions the platform as a testable regenerative strategy rather than an established treatment for age-related muscle loss. Translation of integrated regenerative interventions for sarcopenia requires a staged evidentiary framework linking product identity, molecular target engagement, tissue-specific biological activity, and functional outcomes. Initial development should prioritize reproducible manufacturing, compositional characterization, and mechanism-linked potency assays. Subsequent studies should determine whether biological effects observed in isolated cells persist in multicellular muscle models and translate into improvements in muscle structure and contractile performance. Experimental models must reflect the intended indication. Acute injury, glucocorticoid-induced atrophy, disuse, denervation, cancer cachexia, and age-related sarcopenia share selected pathways but differ in pathophysiology. Findings from one model should therefore not be generalized to another without disease-relevant confirmation. Studies of aging-associated muscle loss should preferentially incorporate aged animals or human-derived systems representing the metabolic, inflammatory, and regenerative characteristics of older muscle. Clinical evaluation should distinguish mechanistic target engagement from clinically meaningful benefit. Muscle quantity, mitochondrial biomarkers, and molecular signaling responses provide supportive evidence but are insufficient as standalone measures of efficacy. Contemporary regulatory discussions emphasize validated assessments of muscle strength and physical performance, including gait speed, the Short Physical Performance Battery, stair-climb performance, and walking capacity [30]. Imaging-derived muscle quantity and quality may complement these measures but should not replace functional evaluation.

Novel regenerative interventions must also be evaluated within the context of established sarcopenia

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management. Resistance exercise and appropriate nutritional support remain central therapeutic approaches, with evidence supporting improvements in muscle strength, mass, and physical function [31]. Accordingly, early clinical studies should control for exercise exposure, dietary protein intake, baseline functional impairment, comorbidities, and concurrent medications. Candidate biologics should initially be evaluated as potential adjuncts rather than replacements for established interventions. Safety requirements must reflect the composition and mechanism of each modality. Cellular preparations require assessment of proliferative behavior, inappropriate differentiation, biodistribution, and immune compatibility. MO biologics require evaluation of product purity, inflammatory responses, and the consequences of exposure to mitochondrial constituents. NOP preparations require assessment of immunogenicity, off-target activity, dose-dependent effects, and manufacturing consistency. Combination administration introduces additional uncertainties requiring dedicated evaluation. The relevant translational benchmark is therefore not generalized biological activity or increased muscle mass alone, but reproducible improvement in skeletal-muscle strength and physical performance supported by coherent mechanistic evidence and an acceptable safety profile.

Conclusions

Sarcopenia reflects the progressive deterioration of an integrated muscle-maintenance system involving myogenic progenitors, mitochondrial function, neuromuscular integrity, and the regenerative microenvironment. These interacting constraints limit both the preservation of existing myofibers and the capacity to generate functional replacement tissue. Accordingly, muscle regeneration requires more than stimulation of hypertrophy or modification of isolated metabolic pathways. A systems-regeneration framework integrating myogenic precursor/progenitor approaches, mitochondrial-directed therapeutics, and peptide-mediated signaling provides a biologically grounded strategy for investigating complementary regenerative mechanisms. The EW platform represents one candidate implementation of this architecture, but existing platform-specific evidence remains insufficient to establish therapeutic efficacy in sarcopenia. Further development should prioritize molecular product characterization, mechanism-linked potency assays, disease-relevant human muscle models, factorial combination studies, and controlled clinical evaluation. The central objective is durable restoration of metabolically competent, appropriately innervated skeletal muscle capable of generating meaningful force and improving physical function.

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