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Review Article

Organ-Specific Precursor Stem Cell Transplantation, Mitochondrial Organelle and Peptide Administration, and Nano-Organ peptides: Routes, Mechanisms, and Clinical Translation

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Abstract

This review examines three emerging therapeutic modalities at the intersection of regenerative medicine, mitochondrial biology, and nanomedicine: (i) organ-specific progenitor cell delivery, (ii) mitochondrial transplantation and Mitochondrial-Derived Peptide (MDP) administration, and (iii) nanoformulated organelle-targeted peptides. Although each approach has been investigated independently, their potential conceptual integration has not been systematically evaluated. We synthesize current evidence regarding mechanisms of action, routes of administration, pharmacokinetics, and translational status across these domains. For progenitor cell therapies, available clinical data suggests that therapeutic effects are largely mediated through paracrine signaling rather than durable engraftment, with delivery route influencing biodistribution and retention. Mitochondrial transplantation has demonstrated bioenergetic rescue in preclinical models and in limited clinical contexts, although its durability, scalability, and immunological implications remain incompletely characterized. MDPs and related peptide systems exhibit pleiotropic cytoprotective and metabolic effects in experimental systems but are constrained by pharmacokinetic limitations that have motivated the development of nanoparticle-based delivery platforms. Across modalities, evidence remains heterogeneous and is predominantly derived from preclinical studies or early-phase clinical investigations.

We therefore propose a conceptual, tiered framework in which these strategies target complementary aspects of tissue dysfunction, structural cellular deficits, bioenergetic impairment, and dysregulated signaling, while emphasizing that this framework is hypothesis-generating rather than clinically validated. Key translational challenges include standardization of potency assays, optimization of delivery routes, long-term safety assessment, and regulatory alignment for combination advanced therapies. Future progress will depend on rigorously designed comparative and combinatorial studies to determine whether integration of these approaches provides additive or synergistic benefit beyond individual modalities.

Keywords: Organ-specific stem cells, Precursor cells, Intramuscular injection, Mitochondrial transplantation, Mitochondrial-derived peptides, Nano-organ peptides, Regenerative medicine

Introduction

Degenerative diseases of the heart, liver, kidney, skeletal muscle, and Central Nervous System (CNS) share a common pathophysiological path, i.e., the progressive exhaustion of tissue-resident progenitor populations [1]. coupled with mitochondrial dysfunction [2] and the loss of intercellular trophic signaling [3]. Conventional pharmacotherapy addresses downstream symptoms of the degeneration rather than the upstream erosion of regenerative capacity [4]. However, over the past two decades, three broad technological families have emerged to address this deficit at its root. First, organ-specific precursor stem cells, e.g., Cardiac Progenitor Cells (CPCs), hepatic oval cells, renal Parietal Epithelial Stem Cells (PESCs), and Skeletal Muscle Satellite Cells (SCs), can be isolated, expanded ex vivo, and re-administered by Skeletal Muscle Satellite Cells (SCs) injection to exploit local paracrine niches and facilitate engraftment [5-7]. Second, the recognition that mitochondria retain partial autonomy and can be transferred between cells both physiologically (via tunneling nanotubes and extracellular vesicles) and therapeutically (via injection of isolated organelles) has contributed to the emergence of a field often termed "mitochondrial medicine [8]. Concurrently, small mitochondrial open reading frame-encoded peptides, collectively termed Mitochondrial-Derived Peptides (MDPs), have been identified as potent cytoprotective and metabolic regulators with pharmacological tractability [9-11]. Third, the convergence of peptide chemistry with Lipid Nano Particles (LNPs), self-assembling protein nanocages, and exosome-mimetic vesicles have yielded nano-organ peptide platforms capable of bypassing first-pass metabolism and enabling sublingual bioavailability for otherwise labile macromolecules [12,13]. This review provides an integrated analysis of all three modalities with specific attention to route of administration, biodistribution, mechanism of action, clinical evidence, and safety. We address gaps in current knowledge and identify the experimental and regulatory steps required to advance each strategy toward broad clinical adoption.

Organ-Specific Precursor Stem Cells: Biology and IM Delivery

Tissue-specific stem and progenitor cells occupy a phenotypic space between pluripotent stem cells and fully differentiated progeny [14,15]. Their utility for cell therapy depends on balancing proliferative capacity against commitment to a target lineage. (Table 1) summarizes the major organ-specific precursor populations evaluated in clinical or advanced preclinical contexts.

Table 1: Representative organ-specific progenitor cell types evaluated in regenerative medicine, with defining markers and clinical trial references (if available0.

Cell Type	Source Tissue	Key Surface Markers	Primary Differentiation Potential	Example of Clinical Trials
Cardiac Progenitor Cells (CPCs) [16]	Myocardial biopsy	c-Kit+, Sca-1+, CD105+	Cardiomyocytes, smooth muscle, endothelium	SCIPIO, CADUCEUS (NCT00474461)
Hepatic Progenitor / Oval Cells [17]	Liver biopsy, cord blood	EpCAM+, AFP+, CK7+, CD90+	Hepatocytes, cholangiocytes	Multiple Phase I/II (liver cirrhosis)
Renal PESCs	Urine, renal biopsy	CD24+, CD133+, Wt-1+	Podocytes, proximal tubule cells	Preclinical18
Skeletal Muscle Satellite Cells (SCs) [19]	Muscle biopsy	Pax7+, CD56+, M-Cadherin+	Type I/II myofibers	Duchenne MD trials (Phase I/II)
Neural Progenitor Cells (NPCs) [20]	SVZ biopsy, iPSC-derived	Nestin+, SOX2+, CD133+	Neurons, astrocytes, oligodendrocytes	StemCells Inc. ALS trial
Pancreatic Progenitors [21]	Ductal tissue, iPSC-derived	PDX1+, SOX9+, NKX6.1+	β-cells, ductal cells	ViaCyte ClinicalTrials NCT02239354
Endothelial Progenitor Cells (EPCs) [22]	Peripheral blood, bone marrow	CD34+, KDR+, CD31+	Mature endothelium, angiogenesis	REPAIR-AMI (NCT00279175)

Rationale for Intramuscular (IM) vs. Intravenous (IV) Delivery

The optimal route of stem cell administration remains contested. IV delivery of stem cells offers systemic distribution but is complicated by pulmonary first-pass trapping, rapid immune clearance, and poor homing efficiency to non-vascular targets, which are estimated that less than 1–5% of administered cells reach intended organs [23–25]. Intra-arterial delivery improves targeting but carries embolic risk [26,27]. Direct intramyocardial or intraportal injections achieve high local concentrations at the cost of invasive procedures [28]. IM injection has been proposed as a potentially practical alternative for several progenitor cell types, particularly CPCs and myogenic progenitors. Key mechanistic arguments include: (a) the rich capillary and lymphatic bed within skeletal muscle facilitates staged cell release into systemic circulation28 ; (b) the IM environment provides integrin-binding ECM substrates (laminin, fibronectin, collagen IV) that enhance short-term cell viability [29] ; (c) satellite cell niches within skeletal

muscle secrete Hepatocyte Growth Factor (HGF), insulin-like growth factor-1 (IGF-1), and stromal cell-derived factor-1 (SDF-1/CXCL12), each of which supports the survival and migration of co-administered heterologous progenitors [30] ; and (d) repeated IM boluses enable dose titration without central venous access. Preclinical models demonstrate that IM-delivered CPCs in murine infarct models achieve cardiac homing rates of 3–8% over 72 hours, in which the CXCR4–SDF-1α axis appears to play an important, though not exclusive, role [31]. Huang et al. (2021) demonstrated that IM injection of human hepatic progenitors into the quadriceps of NOD/SCID mice bearing CCl_4-induced cirrhosis led to a 2.3-fold improvement in serum albumin versus IV controls, attributed to slower kinetics of progenitor mobilization and reduced pulmonary trapping [32].

Homing Mechanisms: Receptor-Ligand Networks

Effective therapeutic homing requires engagement of chemokine gradients established by injured target tissue. The SDF-1α/CXCR4 axis is the best characterized: damaged parenchyma upregulates SDF-1α secretion, establishing a chemotactic gradient that directs CXCR4-expressing progenitors toward the lesion [33]. Genetic or pharmacological pre-conditioning of donor cells with CXCR4 overexpression consistently improves engraftment in myocardial, renal, and hepatic models [34,35]. Additional relevant axes include: (a) HGF/c-Met, critical for hepatic and renal progenitor homing [36]; (b) HMGB1/RAGE and HMGB1/CXCR4, operative in post-ischemic myocardium [37]; (c) P-selectin/PSGL-1-mediated rolling adhesion at inflamed endothelium [38]; (d) the sphingosine-1-phosphate (S1P)/$S1P_1$ receptor gradient, which modulates egress from skeletal muscle IM depots [39]. Engineering strategies, e.g., surface conjugation of targeting ligands, hypoxic preconditioning to upregulate HIF-1α and downstream CXCR4, small-molecule priming with SDF-1α analogs, have each been shown to enhance IM-to-organ transit efficiency by 40–300% in preclinical systems [40,41].

Paracrine Mechanisms and Trophic Signaling

The therapeutic benefit of progenitor cell transplantation increasingly appears to depend less on direct cell replacement (engraftment efficiencies rarely exceed 1–3% at 30 days in clinical settings) and more on the secretion of a complex paracrine secretum. This “paracrine hypothesis” suggests that growth factors, cytokines, EVs, and non-coding RNAs [42,43,44], fundamentally reframes the goal of cell therapy from cellular repopulation to tissue-level signal restoration. Key paracrine mediators secreted by IM-injected progenitors include: VEGF-A (pro-angiogenic), HGF (anti-apoptotic, pro-regenerative), IGF-1 (anti-atrophic), TGF-β1 (anti-fibrotic in low concentrations), IL-10 (immunomodulatory), and a diverse cargo of microRNAs packaged within exosomes [45]. For example, miR-21, miR-146a, and miR-210 species have each been identified as cardioprotective mediators transferred from CPCs to cardiomyocytes via exosomal pathways [46]. and in skeletal muscle models, EV-mediated transfer of miR-206 from transplanted satellite cells to host myofibers promotes myogenic gene expression (MyoD, myogenin, MHC-IIa) and fiber hypertrophy [47]. This paradigm shift provides the conceptual foundation for the cell-free and peptide-based therapeutic tiers reviewed in subsequent sections, which seek to replicate and amplify these paracrine signals without the logistical and immunological constraints of viable cell delivery.

Clinical Evidence for IM-Delivered Organ-Specific Progenitors

Cardiac Applications

The SCIPIO trial enrolled 33 patients with ischemic cardiomyopathy and demonstrated that intracoronary infusion of autologous c-Kit+ CPCs improved Left Ventricular Ejection Fraction (LVEF) by 8.2 percentage points at 12 months, with reduction in infarct size [48]. While subsequent independent analyses raised methodological concerns about the data, independent mechanistic studies in non-human primates confirmed the secretome-mediated benefit. The CADUCEUS trial [49]. using cardio sphere-derived cells (CDCs) via IC injection reported a 42% relative reduction in scar mass at 12 months. IM delivery of CPCs has been evaluated in Peripheral Artery Disease (PAD) models as a surrogate for cardiac applications. Losordo et al. (2011) conducted a Phase II randomized trial (NCT00108810) of IM-delivered CD34+ cells in no-option angina patients (n=167), demonstrating significant reduction in angina frequency and improved exercise tolerance at 12 months [50].

Hepatic Applications

Multiple Phase I and II trials have evaluated portal vein, splenic artery, and peripheral IV infusion of autologous or allogeneic hepatic progenitors in liver cirrhosis, with findings generally indicating modest improvements in hepatic synthetic function, e.g., serum albumin bilirubin, alongside acceptable short-term safety profiles, though trial heterogeneity in cell source, dose, and route limits cross-study comparison [51]. The evidence base at present consists predominantly of small, uncontrolled Phase I studies. To date, adequately powered randomized controlled trials with standardized endpoints remain absent from the literature, and conclusions regarding efficacy must therefore be regarded as preliminary. IM delivery of hepatic progenitors is investigational at this stage, without published controlled human data, but offers theoretical practical advantages for repeat outpatient dosing relative to portal or splenic arterial routes, which require interventional radiological access and carry procedure-associated risk [52]. The depot pharmacokinetics of IM administration may be particularly relevant to hepatic indications given the gradual progenitor mobilization kinetics observed in preclinical models, warranting dedicated clinical evaluation.

Muscular Dystrophies

Myoblast Transplantation (MT) trials for Duchenne Muscular

Dystrophy (DMD) have been conducted since the 1990s with variable outcomes [53]. The failure of early trials was attributed to immune rejection, poor cell survival, and limited migration from IM injection sites [54]. More recent approaches using satellite cell-enriched populations, immunosuppression, and hydrogel encapsulation have demonstrated dystrophin restoration in 6–15% of fibers at injection sites [55]. The CARE-MD trial (NCT03362502) evaluated IM-delivered myogenic progenitors in limb-girdle muscular dystrophy Type 2I with promising Phase I safety data.

Safety Considerations and Immunological Barriers

The principal safety concerns for organ-specific progenitor cell therapy via IM injection include: (1) ectopic tissue formation, particularly teratoma risk with pluripotent-derived cells (mitigated by use of committed progenitors); (2) immunological rejection of allogeneic cell products despite MHC matching; (3) pro-arrhythmic risk with cardiac progenitors engrafting in conduction tissue; (4) theoretical oncogenic risk, particularly with c-Kit+ populations and extended ex vivo expansion [56]. Long-term surveillance data from trials with follow-up exceeding five years are reassuring. To date, no de novo tumor formation has been reported in available follow-up periods; however, long-term surveillance data remain limited.

Mitochondrial Organelles and Mitochondrial-Derived Peptides: IM and IV Delivery

Mitochondria are semi-autonomous organelles of endosymbiotic origin, maintaining a 16.6 kb circular genome (mtDNA) encoding 13 essential oxidative phosphorylation (OXPHOS) subunits, 22 tRNA species, and 2 rRNA species [57]. Their primary functions encompass ATP synthesis via the electron transport chain (ETC), regulation of intracellular calcium homeostasis, Reactive Oxygen Species (ROS) generation and scavenging, thermogenesis, and coordination of intrinsic apoptosis [58]. Dysfunctional mitochondria are implicated in the pathogenesis of ischemia-reperfusion injury, heart failure, Parkinson disease, Non-Alcoholic SteatoHepatitis (NASH), type 2 diabetes, sarcopenia, and accelerated cellular senescence [59–61]. The discovery of intercellular mitochondrial Transfer Via Tunneling Nanotubes (TNTs), gap junctions, EVs, and direct cell fusion established the conceptual basis for therapeutic mitochondrial transplantation [62]. Hayakawa et al. (2016) demonstrated in an astrocyte-neuron co-culture model that astrocytes release mitochondria into EVs that are subsequently engulfed by ischemic neurons, rescuing their bioenergetic capacity [63]. That a physiological intercellular rescue mechanism, refined over evolutionary timescales, can be deliberately operationalized as a therapeutic intervention represents one of the most conceptually significant developments in modern regenerative medicine, transforming the mitochondrion from a passive target of pharmacological intervention into an active, transplantable therapeutic unit.

Isolation of mitochondria for experimental or therapeutic use typically involves differential centrifugation of homogenized tissue, often followed by density gradient purification to reduce contamination from other organelles [64]. Assessments of mitochondrial integrity and function commonly include measurement of membrane potential, oxygen consumption rate, and structural integrity assays [65]. However, there is currently no universally accepted standard for defining mitochondrial "potency" in a therapeutic context, and variability in isolation and quality control methods complicates comparison across studies.

Exogenous mitochondria have been reported to enter recipient cells through multiple uptake pathways, including macropinocytosis, clathrin-mediated endocytosis, and action-dependent processes [66]. The relative contribution of these mechanisms appears to vary by cell type and experimental conditions. Molecular determinants of uptake, including the roles of outer membrane proteins and lipid components, remain an area of active investigation, and a unified mechanistic model has not yet been established [67].

IM versus IV Pharmacokinetics

Following IV administration in animal models, exogenous mitochondria are rapidly cleared from circulation, with preferential accumulation in the liver, lung, and spleen [68]. Reported plasma half-lives are on the order of minutes, although these estimates vary depending on labeling strategy and detection method [69]. Limited evidence suggests that a small fraction of administered mitochondria may be localized to injured tissues, including ischemic myocardium, but the efficiency and functional relevance of this process remain uncertain [70]. IM administration has been proposed as an alternative delivery route that may result in higher local tissue retention and more gradual systemic distribution via lymphatic and vascular pathways [71]. Preclinical studies have reported increased local mitochondrial concentrations following intramuscular injection compared with intravenous delivery [72]. However, whether such depot-like effects translate into improved therapeutic outcomes in clinically relevant settings has not been established.

Despite clinical potential [73], clinical investigation of mitochondrial transplantation remains limited. The most extensively described applications involve intraoperative administration of autologous mitochondria during pediatric cardiac surgery in small patient series [74]. These reports suggest that mitochondrial administration may be feasible and associated with short-term functional improvement in highly specific contexts [75]. However, these findings are based on small, non-randomized cohorts and should be interpreted cautiously. Early-phase studies exploring intramuscular mitochondrial administration in adult populations have reported evidence of mitochondrial uptake by circulating cells and potential systemic redistribution. The clinical significance, reproducibility, and durability of these observations remain to be determined, and controlled trials are lacking.

MDPs: Biology and Pharmacology

The identification of short open reading frames within mitochondrial and nuclear genomes encoding bioactive peptides

has substantially expanded current understanding of mitochondrial signaling, repositioning the mitochondrion as an active endocrine organ rather than a passive metabolic compartment [76,77]. MDPs have been implicated in the regulation of metabolic homeostasis, stress responses, and cell survival pathways across experimental systems, and their therapeutic potential has been systematically characterized in translational reviews drawing on both mechanistic and applied clinical evidence [73,78]. The broader functional significance of mitochondrial organelles as master regulators of cellular wellness integrating bioenergetic, redox, calcium, and immune signaling, provides the systems-level context within which individual MDP mechanisms must be interpreted [79]. Humanin, one of the earliest described MDPs, is encoded within the 16S rRNA region of the mitochondrial genome and was originally identified through functional screening of an occipital lobe cDNA library from Alzheimer disease patients [80]. Humanin interacts with multiple receptor systems, e.g., gp130/LIF receptor/CNTFR tripartite complex, FPRL1, and intracellular IGFBP3, activating STAT3, MAPK, and AKT survival pathways [80,81]. In preclinical models, humanin and its analogs have been associated with cytoprotective effects across myocardial, neurodegenerative, diabetic, and oncological disease contexts [82,83], though most evidence derives from vitro or animal studies and clinical data remain limited. The therapeutic relevance of humanin signaling to neurodegenerative disease has been examined in dedicated translational analyses addressing both pathophysiological mechanisms and emerging regenerative treatment strategies [84,85]. The analog HNGF6A, with Gly6→Phe substitution and C-terminal amidation, exhibits approximately 1,000-fold greater receptor binding potency than native humanin [86]. Humanin serum levels decline by approximately 40% between ages 20 and 60, implicating it as an endocrine mediator of age-related disease susceptibility [87]. Its cytoprotective relevance to cardiac aging and peptide-mediated prevention of mitochondrial dysfunction and fibrosis has been further characterized in indication-specific analyses [88,89].

MOTS-c, a 16-amino acid peptide encoded within the 12S rRNA region of the mitochondrial genome, influences metabolic regulation principally through nuclear translocation and AMPK activation, with downstream suppression of de novo purine synthesis via AICAR accumulation and induction of the folate cycle [77]. MOTS-c sensitizes skeletal muscle to insulin-stimulated glucose uptake by derepressing GLUT4 translocation via AMPK-AS160 phosphorylation [90]. MOTS-c levels decline with age and are lower in individuals with metabolic syndrome and type 2 diabetes [91]. Exercise represents a potent physiological induce of MOTS-c secretion from skeletal muscle mitochondria, positioning it as a mitokine that partially mediates the systemic metabolic benefits of physical activity [91]. IM administration of MOTS-c in aged mice has been shown to restore exercise capacity and reduce markers of inflammaging including TNF-α, IL-6, and NF-κB nuclear translocation [76]. The translational significance of MOTS-c and related multi-organ peptides to metabolic syndrome has been addressed in dedicated analyses examining both mechanistic networks and therapeutic frameworks [92]. The musculoskeletal and neuromuscular dimensions of metabolic syndrome prevention, within which the exercise-mimetic properties of MOTS are particularly relevant, have been further characterized in dedicated translational work [93]. As with other MDPs, robust randomized clinical trial data for MOTS-c in human disease remain absent, and translation of experimental findings to clinical practice requires cautious interpretation.

Small humanin-like peptides (SHLPs 1–6), encoded within the mitochondrial 16S rRNA region, share partial structural homology with humanin but exhibit distinct receptor engagement profiles with organ-specific pharmacodynamic relevance [78]. SHLP-2 has demonstrated potent anti-apoptotic and pro-angiogenic effects in retinal pigment epithelium, positioning it as a candidate for age-related macular degeneration and related retinal degenerative conditions [82]. SHLP-3 reduces mitochondrial superoxide generation and preserves cristae morphology in hepatocytes exposed to palmitate-induced lipotoxicity, with relevance to non-alcoholic steatohepatitis pathophysiology [78]. Their application to retinal disease has been examined in the context of peptide-based immune recalibration strategies for vision preservation [94], and their relevance to renal peptide therapeutics has been addressed in the context of nano-organo and mitochondria-targeted strategies for kidney disease [95]. The potential of SHLP and human-in-family peptides in intestinal mucosal regeneration has been examined in barrier-focused peptide analyses [96].

SS-peptides, synthetic tetrapeptides designed by Szeto and Schiller to concentrate approximately 5,000-fold at cardiolipin microdomains on the inner mitochondrial membrane, scavenge locally generated ROS, prevent cytochrome c peroxidation, stabilize cristae architecture by promoting ATP synthase dimer polymerization, and restore electron transport chain super complex assembly [97,98]. SS-31 (elamipretide; D-Arg-dimethyl Tyr-Lys-Phe-NH_2) is the most clinically advanced agent in this class, having received FDA Fast Track designation for Barth syndrome (NCT02814097) and Duchenne cardiomyopathy, and having demonstrated a 44% reduction in acute kidney injury in Phase II evaluation (Mitochondria in Acute MI and Reperfusion Damage [MMAD] study, NCT01015170) [99]. IM administration of SS-31 in mdx dystrophic mice reduced diaphragm fibrosis and improved specific force generation, highlighting its relevance to musculoskeletal applications of mitochondrial-targeted peptide therapy [100]. Across all MDP classes, the convergence of short peptide length, multi-receptor engagement, and mitochondrial targeting capacity supports the thesis that short peptides may represent a pharmacologically viable and physiologically resonant approach to longevity and disease-modification goals, provided that delivery optimization and clinical trial infrastructure are adequately developed.

Pharmacokinetic Considerations

MDPs are subject to rapid degradation and clearance,

presenting challenges for therapeutic application. Strategies to improve stability and bioavailability include peptide modification, conjugation, and encapsulation within delivery systems. IM administration may result in slower systemic absorption compared with intravenous delivery, although comparative pharmacokinetic data are limited and formulation dependent. Overall, while mitochondrial transplantation and MDP-based interventions represent promising areas of investigation, their clinical utility remains to be established. Key uncertainties include optimal delivery strategies, durability of effect, safety in larger populations, and reproducibility across disease contexts.

Nano-Organ peptides: Design, Routes of Administration, and Clinical Perspectives

The term "nano-organ peptide" as used in this review encompasses nanoscale delivery vehicles that encapsulate or surface-conjugate biologically active peptides derived from, or targeting, subcellular organelles, primarily mitochondria, lysosomes, the endoplasmic reticulum, and the nucleus. These constructs are designed to address limitations such as: (a) protection from proteolytic degradation; (b) prolonged circulation time; (c) cell-specific uptake via receptor-mediated endocytosis; (d) endosomal escape capability; and (e) stimulus-responsive release, although the extent to which these advantages are realized in vivo varies across systems [101].

Nanoparticle Platform Classes

LNPs

LNPs comprising ionizable lipids, phospholipids, cholesterol, and PEG-lipids, the platform underlying approved COVID-19 mRNA vaccines, are the most clinically advanced nanoparticle system for biological payload delivery. For peptide applications, LNP formulations offer high encapsulation efficiency (>80% for cationic peptides), endosomal escape via pH-responsive ionizable lipid membrane fusion, and scalable GMP-compatible manufacturing [102,103]. LNP-encapsulated MOTS-c demonstrated 4.7-fold greater hepatic accumulation versus free peptide in a murine NASH model, with commensurate improvement in hepatic lipid content and ALT normalization, attributed to apolipoprotein E-mediated hepatic uptake of PEGylated LNP surfaces [77,104]. IV-administered LNP-MOTS-c induced hepatic AMPK activation within four hours compared with a 12-hour delay for IM free peptide, underscoring the route-dependent pharmacodynamic timing that must be considered in clinical protocol design [91].

Exosome-Mimetic Nanoparticles and EVs

Native EVs carry an endogenous cargo of MDPs, miRNAs, and mitochondrial proteins and exploit conserved intercellular communication pathways for cell-specific uptake [105]. Engineering EVs to overload specific MDP cargo has produced exosome-based nano-organ peptide systems with enhanced and tunable potency [106]. Subcutaneous and IV routes have been evaluated for EV-based delivery systems; sublingual absorption of EV formulations has been demonstrated for miRNA-loaded exosomes in rodent models, with bioavailability dependent on vesicle surface charge and mucoadhesive properties [107].

Polymeric Nanoparticles: PLGA and PLA-PEG

Poly (lactic-co-glycolic acid) (PLGA) nanoparticles offer biodegradable, tunable release kinetics governed by polymer molecular weight and lactide: glycolide ratio and are incorporated into multiple FDA-approved injectable formulations [108]. PLGA-encapsulated humanin analogs (HNGF6A-PLGA) demonstrated sustained in vitro release over seven days and significantly improved 30-day survival in a murine model of sepsis-induced multiorgan failure versus free peptide bolus, attributed to maintenance of therapeutic plasma concentrations beyond the acute inflammatory window [86]. IM depot formulations of PLGA-MOTS-c in nonhuman primates yielded measurable plasma levels for 14 days from a single injection, demonstrating the feasibility of extended-release MDP administration without repeat parenteral access91.

Self-Assembling Peptide Nanostructures

Amphiphilic peptide amphiphiles (PAs) and beta-sheet fibril-forming sequences self-assemble under physiological conditions into nanotubes, vesicles, or hydrogels that embed bioactive peptide epitopes within their supramolecular architecture, enabling sustained local delivery from IM injection depot sites while preserving receptor-binding conformation [109]. Silva et al. demonstrated that IM injection of IKVAV PA nanofibers, incorporating the laminin-derived neural homing pentapeptide sequence, in a murine thoracic spinal cord injury model promoted motor neuron axonal regeneration and behavioral recovery equivalent to cellular transplantation approaches, through selective engagement of integrin receptors on neural progenitor cells [110].

Sublingual Delivery of Nano-Organ peptides

The sublingual route offers rapid systemic absorption via the sublingual venous plexus, bypassing hepatic first-pass metabolism, combined with ease of self-administration, high patient compliance, and suitability for chronic repeat dosing of labile peptide therapeutics that would be impractical to administer repeatedly by injection in outpatient settings [111]. The sublingual oral mucosa permits molecular transit within 1–3 minutes on average, driven by passive diffusion for small lipophilic molecules and carrier-mediated transport for larger hydrophilic species, with the sublingual epithelium, i.e., non-keratinized, 50–100 μm in thickness, offering greater permeability than buccal or palatal mucosa [112]. Native MDPs pose significant sublingual bioavailability challenges: tight junctions restrict paracellular transport of hydrophilic macromolecules, and salivary proteases rapidly cleave peptide bonds, yielding plasma bio availabilities below 5% for unmodified peptide sequences [113]. Nanoparticle encapsulation addresses these barriers through multiple complementary mechanisms: mucoadhesive surface coatings extend sublingual residence time

from seconds to 5–30 minutes by forming non-covalent interactions with mucin glycoproteins [114].

De Vos et al. (2023) demonstrated that chitosan-coated LNPs carrying MOTS-c achieved sublingual bioavailability of 34% versus 2.1% for unencapsulated peptide in Sprague-Dawley rats, with plasma half-life extended from 8 to 47 minutes, attributable to combined mucoadhesion, protease shielding, and transcellular uptake via chitosan-mediated tight junction modulation. [115] Zhang et al. discussed the efficacy of mitochondria-targeted nano systems in rescuing mitochondrial dysfunction across major CNS conditions highlighting current translational challenges and future research directions pivotal for advancing mitochondrial nanomedicine. Collectively, this work synthesizes progress in mitochondrial nanotherapeutics, highlighting their transformative potential while outlining critical barriers and opportunities for clinical translation in CNS disorders [116] (Table 2).

Table 2: provides a structured comparison of the three primary delivery routes for nano-organopeptide systems based on available preclinical and clinical data.

Parameter	IM Injection	IV Injection	Sublingual
Onset of action	20-60 min (depot release)	2-15 min (rapid)	5-20 min (mucosal)
Peak plasma (Tmax)	60-180 min	5-30 min	20-60 min
Bioavailability (nano formulated)	70-90%	100% (reference)	25-50% (formulation-dependent)
First-pass avoidance	Yes (lymphatic)	Yes (IV)	Yes (sublingual vein)
Hepatic targeting	Poor	Excellent	Moderate
Cardiac targeting	Moderate (lymphatic homing)	Good (with active targeting)	Low (no active targeting)
CNS penetration	Poor (native)	Depends on BBB strategy	Low-moderate (CPP enhanced)
Duration of effect	12-72 h (biodegradable depot)	2-24 h (standard)	4-12 h
Patient acceptability	Moderate (requires injection)	Low (IV access needed)	High (self-administered)
Regulatory precedent	Multiple approved injectables	Multiple approved	Limited peptide precedents

Beyond peptide identity, the subcellular destination of nano-organ peptide payload profoundly determines pharmacodynamic outcome. Four primary organelle targeting strategies are established.

a) Fusion of N-terminal amphipathic to therapeutic cargo directs uptake through the translocase of the outer membrane and translocase of the inner membrane (TOM/TIM) import machinery, achieving intra-matrix delivery with high selectivity over cytosolic retention [117]. The specificity of MTS-mediated targeting is conferred by the amphipathic helical structure of the presequence, which is recognized by the TOM20 receptor subunit and processed by the mitochondrial processing peptidase (MPP) following import [118]. This approach has been applied to redirect catalase to the mitochondrial matrix, where its expression reduced H_2O_2-mediated oxidative stress by 85% and extended median lifespan by 20% in aged transgenic mice [119]. MTS fusion strategies have since been extended to superoxide dismutase-2 analogs, mitochondrially targeted antioxidant peptides, and gene editing constructs intended for mtDNA correction120.

b) Nanoparticles surface-functionalized with SS-31 moieties have been demonstrated to achieve selective mitochondrial membrane binding with significantly reduced lysosomal accumulation compared with untargeted formulations, overcoming the predominant endolysosomal sequestration that limits the intracellular efficacy of conventional nanoparticle systems [121]. The cardiolipin-anchoring strategy has been applied to co-deliver coenzyme Q10 analogs and cytochrome c stabilizers in models of ischemia-reperfusion injury, Parkinson disease, and Barth syndrome-associated cardiomyopathy [122].

c) KDEL-sequence decoration, exploiting the endogenous KDEL receptor-mediated retrieval pathway that returns escaped ER-resident proteins from the Golgi to the ER lumen, redirects nanoparticle endosomal escape toward the ER rather than the cytosol, enabling delivery of unfolded protein response (UPR) modulators including salubrinal-peptide conjugates and IRE1α inhibitors to their site of action [123]. Salubrinal, a selective inhibitor of eIF2α dephosphorylation that reduces ER stress-induced apoptosis, has demonstrated neuroprotective, cardiomyocyte-protective, and chondroprotective effects in preclinical models when delivered to the ER lumen via KDEL-decorated polymeric nanoparticles, with efficacy superior to free drug administration attributable to organelle-level payload concentration [124].This targeting strategy is of particular relevance to degenerative conditions characterized by chronic proteotoxic ER stress where sustained UPR activation drives

parenchymal cell loss and fibrotic remodeling [125].

d) Nuclear Localization Sequence (NLS) functionalization enables receptor-mediated importin-α/β-dependent nuclear import of nanoparticle cargo, facilitating non-viral delivery of DNA repair peptides, transcription factor analogs, and epigenetic modulators to the nucleus [126]. NLS-functionalized poly(lactic-co-glycolic acid) nanoparticles carrying p53-activating peptides have demonstrated selective nuclear accumulation and pro-apoptotic activity in hepatocellular carcinoma models, with a 3.4-fold improvement in nuclear delivery efficiency versus non-functionalized controls [127].

Synergistic Combination Strategies: A Conceptual Framework

The integration of organ-specific progenitor cell transplantation, mitochondrial transfer, and nano-organ peptide delivery has been proposed as a multi-layered therapeutic strategy targeting complementary aspects of tissue degeneration. Conceptually, these approaches may be organized into a hierarchical framework addressing (i) structural cellular deficits, (ii) bioenergetic dysfunction, and (iii) dysregulated molecular signaling.

I. Tier 1 — Structural Reconstitution. IM delivery of lineage-committed progenitor cells may partially restore tissue-resident cell populations and provide paracrine support via secreted trophic factors and extracellular vesicles. However, clinical data indicates that long-term engraftment remains limited, and therapeutic benefit is likely mediated predominantly through indirect mechanisms.

II. Tier 2 — Bioenergetic Modulation. Mitochondrial transplantation has demonstrated the capacity to transiently augment oxidative phosphorylation in preclinical models and in highly selected clinical settings (e.g., intraoperative cardiac applications). Whether such effects can be sustained, generalized across tissues, or reproducibly achieved in non-surgical contexts remains uncertain.

III. Tier 3 — Molecular Signal Modulation. Mitochondrial-derived peptides and nano formulated peptide systems offer a pharmacologically tractable approach to modulating stress-response pathways, including AMPK, STAT3, and mitochondrial membrane stabilization. While preclinical data are encouraging, human evidence remains limited, and pharmacokinetic constraints (e.g., rapid clearance, tissue targeting) continue to present challenges.

Collectively, these modalities may exhibit complementary interactions in principle. For example, restoration of bioenergetic capacity could enhance progenitor cell survival, while peptide-mediated signaling may optimize the recipient tissue microenvironment. However, evidence supporting such synergistic effects is currently confined to small animal studies with limited statistical power and heterogeneous methodologies. Accordingly, the proposed tiered framework should be interpreted as a hypothesis-generating model rather than a validated therapeutic paradigm. Rigorous evaluation in controlled, adequately powered studies will be required to determine whether combinatorial approaches provide additive or synergistic benefit beyond individual modalities.

Safety, Immunogenicity, and Regulatory Pathway Considerations

Immunological Considerations

Allogeneic progenitor cell products require either HLA matching, immune suppression, or engineering of "universal donor" cells via CRISPR-mediated MHC class I/II knockout and CD47 overexpression to evade natural killer cell-mediated clearance [128]. The CRISPR-edited "stealth cell" approach has advanced to Phase I clinical evaluation (Sana Biotechnology, NCT05286815), representing the leading edge of universal donor cell engineering in human subjects [129]. For autologous cell products, the primary immunological concern is the innate inflammatory response to injection vehicle components, cellular debris, and necrotic cells within the preparation, which activates complement, TLR-mediated signaling, and NLRP3 inflammasome pathways that collectively limit engraftment efficiency [130]. Isolated mitochondria from allogeneic donors trigger innate immune responses through the release of damage-associated molecular patterns (DAMPs), principally mtDNA, which activates TLR9 and the cGAS-STING pathway; N-formyl peptides (fMLP), which engage TLR-4 and formyl peptide receptors; and cardiolipin, a TLR-2 ligand exposed on the outer mitochondrial membrane surface during organelle stress [131]. The cGAS-STING axis in particular has emerged as a critical mediator of sterile inflammation following mitochondrial DAMP exposure, with downstream type I interferon induction capable of compromising both engraftment of co-administered progenitor cells and recipient tissue regenerative capacity [132].

Strategies to mitigate allogeneic mitochondrial immunogenicity include: DNase I treatment to digest surface-adsorbed mtDNA prior to transplantation [133]; UV-C irradiation to fragment extramitochondrial nucleic acid contaminants [134]; surface coating with PolyEthylene Glycol (PEG) or immunosuppressive exosome-derived membranes to reduce pattern recognition receptor engagement [135]; and ultrashort pulse cryopreservation protocols designed to minimize outer membrane disruption and consequent DAMP release during storage and thawing [136]. Autologous mitochondrial sourcing eliminates allogeneic immunogenicity entirely and represents the most immunologically conservative approach to clinical mitochondrial transplantation [74,137].

Outstanding Challenges and Future Directions

Cell therapy products involving ex vivo expansion carry theoretical oncogenic risk from replicative senescence, epigenetic drift, and viral vector integration, requiring regulatory-grade karyotyping, Comparative Genomic Hybridization (CGH), and

in vitro and in vivo tumorigenicity assessment prior to clinical use (FDA. Guidance for Industry: Considerations for the Design, Development, and Analytical Procedures for Phase 1 Studies of Therapeutic Proteins. CBER; 2021; International Conference on Harmonisation. ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. 2011). Regulatory-grade carcinogenicity evaluation of both xenogeneic progenitor cell populations and high-molecular-weight mitochondrial organelle extracts using BALB/C-3T3 cell transformation assays has been published, providing a methodological reference standard for safety programs in this space [138]. MDPs and nano-organ peptides carry substantially lower oncogenic risk, as peptides are catabolized to constituent amino acids and biodegradable nanoparticle scaffolds undergo hydrolytic degradation to non-toxic monomers under physiological conditions [139].

In the US, organ-specific progenitor cell products are regulated under 21 CFR Part 1271 as human cells, tissues, and cellular and tissue-based products (HCT/Ps), or as drug-biologic combinations requiring a Biologics License Application (BLA) where more than minimal manipulation is involved; CBER guidance addresses potency assays, release criteria, and post-marketing surveillance requirements. MDP therapeutics are regulated as new chemical entities or biologics depending on synthesis route, under NDA or BLA pathways respectively [97,140]. Nano-organ peptide combination products require coordinated review by the FDA Office of Combination Products (OCP) involving CDER, CBER, and potentially CDRH, while the EMA's Committee for Advanced Therapies (CAT) applies the Advanced Therapy Medicinal Products (ATMP) framework for cell therapy combinations within European jurisdictions (European Medicines Agency. Guideline on the Quality, Non-clinical and Clinical Aspects of Gene Therapy Medicinal Products. EMA/CAT; 2018.

Despite remarkable preclinical progress, several scientific and translational challenges must be overcome to realize the full potential of these three modalities:

Standardization of Progenitor Cell Potency Assays: The field lacks validated, universally accepted potency assays that predict in vivo efficacy from in vitro measurements. Secretome profiling (multiplex ELISA, proteomics) combined with in vitro co-culture functional assays offer the most promising path toward surrogate potency metrics [141].

Mitochondrial Preservation and Cold Chain: Current mitochondrial transplantation protocols require fresh organelle preparations (viable for 4–6 hours at 4°C), precluding off-the-shelf availability. Lyophilization and vitrification strategies are under active investigation; preliminary data suggest vitrified mitochondria retain >70% OCR after rehydration [142].

Dose Optimization and Biomarker Development: For all three modalities, the therapeutic window is poorly defined. Circulating cell-free mtDNA, MOTS-c and humanin plasma levels, and MitoTracker-labeled EV concentrations represent emerging biomarker candidates for therapeutic drug monitoring [143].

Blood-Brain Barrier Penetration: CNS applications of MDPs and nano-organ peptides require strategies to overcome the BBB. Focused Ultrasound (FUS)-mediated transient BBB opening combined with IV nano-organ peptide administration has shown 15-fold improvement in CNS delivery versus passive transport in murine models [144].

Long-Term Safety and Pharmacovigilance: Human data beyond 2 years for MDP administration and beyond 5 years for organ-specific progenitor cell therapy remain limited. Dedicated long-term follow-up registries are urgently needed.

Manufacturing Scalability and Cost: GMP manufacturing of progenitor cell products currently costs $30,000–$150,000 per patient dose, limiting accessibility. Allogeneic "off-the-shelf" and iPSC-derived approaches are essential to cost reduction. Synthetic MDP manufacturing by Solid-Phase Peptide Synthesis (SPPS) is scalable and cost-efficient, but nano-organ peptide formulation adds complexity requiring specialized excipient GMP capabilities [145].

In conclusion, the convergence of organ-specific progenitor cell transplantation, mitochondrial transfer, and mitochondrial-targeted peptide therapeutics reflects a broader shift toward multi-level interventions in regenerative medicine. Each of these modalities has demonstrated biological activity in experimental systems and, in some cases, early-phase clinical settings. However, the strength and consistency of evidence vary substantially across domains, with much of the current literature remaining preclinical or derived from small, heterogeneous clinical studies. Organ-specific progenitor cell therapies have advanced furthest clinically, yet their mechanisms of action appear to be driven predominantly by paracrine and immunomodulatory effects rather than durable engraftment. Mitochondrial transplantation has shown the capacity to transiently augment bioenergetic function in controlled experimental contexts and select surgical applications, but questions remain regarding delivery efficiency, persistence, immunogenicity, and scalability. Mitochondrial-derived peptides and related nano formulations offer a pharmacologically tractable means of modulating cellular stress responses, although in vivo pharmacokinetics, tissue specificity, and long-term safety profiles are not yet fully characterized. Interpretation of the tiered framework, linking structural cellular support, bioenergetic modulation, and molecular signaling presents a conceptual model intended to organize emerging data rather than as a validated therapeutic strategy. While preclinical studies suggest that these modalities may exert complementary effects, evidence for additive or synergistic benefit in clinically relevant settings is currently limited. Several challenges must be addressed to enable meaningful clinical translation. These include the development of standardized potency assays for cell-based therapies, improved methods for mitochondrial isolation and preservation, and robust pharmacokinetic and biodistribution profiling for peptide-based and nanoparticle systems. In parallel,

the field would benefit from the identification of reliable biomarkers to guide dosing, monitor target engagement, and stratify patient populations. Long-term safety data, particularly for combination approaches, remain sparse and will require systematic evaluation through appropriately designed clinical trials and post-marketing surveillance frameworks. Regulatory considerations are likely to be complex, especially for combination strategies that span biologics, devices, and advanced therapy medicinal products. Harmonization of regulatory pathways, along with scalable manufacturing approaches, will be critical determinants of feasibility beyond early-stage investigation. Taking together, these modalities highlight a potentially important direction in the evolution of regenerative therapeutics, emphasizing coordinated intervention across multiple layers of cellular function. Whether such integrative strategies can deliver clinically meaningful benefit beyond existing approaches remains an open question. Addressing this question will require rigorously designed comparative and combinatorial studies, with careful attention to reproducibility, safety, and clinically relevant endpoints.

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Ethics Declaration

All authors declare that there are no ethical declarations to declare in relation to this manuscript.

Competing Interests

None.

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