Research Article ISSN 2835-6276

American Journal of Medical and Clinical Research & Reviews

Targeted Stem Cell and Peptide-Based Therapeutics for Gut Diseases: Restoring the Stomach and Intestinal Mucosa through Microbiome and Mitochondrial Modulation

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Received: 05 Aug 2025; Accepted: 30 Aug 2025; Published:05 Sep 2025

Citation: Jonathan RT Lakey. Targeted Stem Cell and Peptide-Based Therapeutics for Gut Diseases: Restoring the Stomach and Intestinal Mucosa through Microbiome and Mitochondrial Modulation. AJMCRR. 2025; 4(9): 1-9.

Abstract

Background: *The gastrointestinal (GI) tract is one of the most dynamic tissue environments in the body, requiring constant regeneration to preserve mucosal integrity against microbial, dietary, and inflammatory stressors. When repair mechanisms fail, chronic gut diseases such as inflammatory bowel disease (IBD), gastritis, ulcerative colitis, Crohn's disease, and mucosal injury syndromes emerge. These conditions are increasingly recognized as resulting from the convergence of impaired epithelial regeneration, microbiome dysbiosis, and mitochondrial dysfunction.*

Objective: *To propose and evaluate an integrative therapeutic paradigm that combines organ-specific progenitor stem cells with next-generation peptide therapeutics, particularly nano-organo peptides (NOPs) and mitochondrial-targeted peptides (MO peptides), for mucosal restoration in chronic GI diseases.*

Methods: *A synthesis of recent advances in epithelial progenitor biology, peptide engineering, and microbiome–host crosstalk was undertaken. Mechanistic insights were integrated with translational strategies, focusing on the regenerative potential of stem cell–peptide combinations.*

Results: *Evidence supports that progenitor cell–based therapies enhance epithelial regeneration, while peptide therapeutics, including NOPs and MO peptides, can target organelle dysfunction and restore*

barrier integrity. Together, these approaches act synergistically to repair mucosa, rebalance microbial ecosystems, and restore mitochondrial health. Early preclinical findings suggest feasibility for precision and regenerative interventions that move beyond symptomatic management.

Conclusions: *Restoring the epithelial–microbiome–mitochondrial axis represents a transformative strategy for chronic gut diseases. Integrating progenitor stem cells with engineered peptide therapeutics holds promise to overcome current therapeutic limitations and accelerate translation into clinical practice.*

Introduction

The stomach and intestinal mucosa, i.e., the gastrointestinal (GI) tract, represent continuously regenerating tissues. The GI epithelial mucosa performs essential functions in digestion, nutrient absorption, immune defense, as well as neurochemical signaling. Despite inherent resilience, the GI epithelial tissues remain highly susceptible to cumulative and chronic injury. The "injury" in turn, leads to chronic gut diseases, including inflammatory bowel disease (IBD), gastritis, ulcerative colitis, Crohn's disease, and mucosal injury syndromes. When chronic epithelial repair mechanisms fail, microbiome composition is disrupted, and/or mitochondrial function declines these chronic diseases ensue, which affect millions worldwide and impose profound socioeconomic burdens . Conventional anti-inflammatory strategies, typically encompassing corticosteroids and immunosuppressants, achieve rapid symptomatic control in inflammatory bowel disease but fall short of promoting durable mucosal healing. Corticosteroids effectively suppress acute inflammation through broad inhibition of NF-κB– and STAT-mediated transcriptional programs, yet their impact is largely palliative. Corticosteroids do not restore epithelial barrier integrity, resolve mitochondrial dysfunction, or prevent structural remodeling such as fibrosis. Similarly, thiopurines and calcineurin inhibitors dampen T-cell activation and cytokine production but do not target epithelial bioenergetics, tight-junction assembly, or microbiome–epithelium crosstalk. As a result, relapse rates remain high once therapy is tapered, and long-term use is limited by adverse events including infection, metabolic toxicity, and carcin ogenesis. Biologics such as anti-TNFα and anti-IL-23 therapies also target suppression of inflammation, but do not fundamentally restore epithelial barrier integrity or prevent long-term complications such as fibrosis and neoplasia. These shortcomings highlight a critical therapeutic gap: conventional agents blunt inflammatory cascades but fail to induce the cellular reprogramming and tissue regeneration required for durable mucosal healing. A deeper understanding of why barrier restoration fails has highlighted the central role of the microbiome, with emerging evidence showing that epithelial health is closely coupled to microbial ecology. In this context, dysbiosis emerges as a key driver, leading to altered microbial metabolites, disruption of stem cell niches, and amplification of mucosal injury. Simultaneously, mitochondrial dysfunction in epithelial and immune cells has emerged as a unifying pathophysiological mechanism in IBD and related conditions, impairing cellular metabolism, redox balance, and regenerative capacity . Together, these insights underscore that mucosal failure is not solely the consequence of uncontrolled inflammation but rather the breakdown of an interdependent epithelial–microbial–metabolic axis. This recognition has shifted therapeutic priorities from transient immunosuppression toward strategies that actively re-

store mitochondrial fitness, re-establish host–microbiome symbiosis, and regenerate epithelial lineages—objectives that conventional corticosteroids and immunosuppressants cannot achieve.

Against this backdrop, novel therapeutic strategies have emerged. Organ-specific progenitor stem cells—derived from gastric and intestinal tissues or engineered from pluripotent sources offer opportunities for mucosal regeneration. In parallel, peptide-based therapeutics, particularly nano-organo peptides (NOPs) designed for receptor or organelle targeting, and mitochondrial-targeted peptides (MO peptides), provide molecular tools to restore energy metabolism, reduce oxidative stress, and modulate immune responses. This review explores the convergence of these fields and presents a framework for integrative therapies that combine progenitor cell transplantation with peptide engineering to restore the mucosa–microbiome–mitochondrial axis.

Chronic Gut Diseases: Description & Pathophysiology from a Microbiome Lens

Inflammatory Bowel Disease (IBD)

IBD encompasses chronic, relapsing inflammation driven by an inappropriate immune response to intestinal microbes in genetically susceptible hosts. The core pathophysiological constructs include impaired epithelial barrier (tight junction disruption, mucus defects), altered innate sensing (TLR/NOD pathways), and skewed adaptive immunity (Th1/Th17 polarization; TNF, IL-23/IL-17 axes). Dysbiosis is typical characterized by reduced diversity, depletion of short-chain fatty acid (SCFA) producers (e.g., Faecalibacterium), enrichment of pathobionts and biofilms, shifting luminal metabolites (bile acid pools, tryptophan/indole pathways) and perpetuating inflammation .

Ulcerative Colitis (UC)

Continuous, superficial mucosal inflammation originating in the rectum and extending proximally. Hallmarks: goblet-cell depletion, crypt architectural distortion, crypt abscesses, and barrier loss limited largely to mucosa. Immunology tends toward Th17/Th2-like signatures. Microbiome features include reduced butyrate producers and altered mucus-associated communities, with oxygenation changes at the inflamed surface favoring facultative anaerobes. Clinical phenotype: bloody diarrhea, urgency, increased colorectal neoplasia risk with duration/extent.

Crohn's Disease (CD)

Transmural, discontinuous ("skip") inflammation that can involve any GI segment, with stricturing and penetrating complications. Histology: granulomas (when present), Paneth cell dysfunction; genetics often implicate autophagy and bacterial handling (e.g., NOD2, ATG16L1). Microbiome signatures include enrichment of adherent-invasive E. coli, reduced obligate anaerobes, biofilm formation, and metabolite shifts that impair epithelial energy use and immune regulation. Complications include fistulas, fibrostenosis, and malabsorption.

Gastritis (chronic)

Persistent gastric mucosal inflammation from Helicobacter pylori, autoimmunity (parietal-cell antibodies), chemical/NSAID injury, or bile reflux. Pathways: epithelial injury → altered mucus/acid dynamics → immune activation (Th1/Th17 for H. pylori; autoimmune corpus-predominant injury leads to hypochlorhydria and B12 deficiency). The gastric microbiome is less diverse but modifiable; H. pylori reshapes gastric ecology and carcinogenesis risk via inflammation and genotoxins (e.g., CagA).

Other Mucosal Injury Syndromes

- Microscopic colitis (lymphocytic/collagenous): Watery diarrhea with near-normal endoscopy; immune activation at the epithelial interface, medication and bile-acid links; subtle dysbiosis reported.
- Celiac disease: HLA-DQ2/8–restricted immune response to gluten causing villous atrophy; microbial peptides and transglutaminase interactions may amplify injury.
- Radiation/ischemic injury: ROS, endothelial damage, and barrier failure; secondary dysbiosis perpetuates inflammation and fibrosis.
- Eosinophilic GI disease & chronic drug-induced enteropathy (e.g., NSAIDs): Barrier disruption and type-2 or mixed immune activation; microbiome shifts can modulate severity.

The microbiome represents a causally proximal regulator of mucosal immunity and epithelial health, with microbial metabolites such as SCFAs, bile acids, and indoles directly shaping immune balance, barrier integrity, and host metabolism. Dysbiosis and microbial functions serve as actionable biomarkers for relapse, therapeutic response, and neoplasia risk, while targeted interventions—ranging from ecological modulation (diet, probiotics, live biotherapeutics, FMT, phage therapy) to metabolite supplementation and barrier repair—offer novel therapeutic levers. When combined with host genomics and mucosal profiling, microbiome-based approaches enable precision stratification and endotype-guided treatment. Collectively, systematic evaluation and targeted modulation of the host–microbe–metabolite axis hold promise for achieving durable mucosal healing, steroid-sparing disease control, and reduced long-term complications across chronic gut disorders.

Pathophysiology of Gut Diseases in the Microbiome Era

Disruption of mucosal integrity

The gut mucosa is the first line of defense against luminal antigens. Tight junction proteins, mucus layers, and epithelial turnover maintain barrier integrity. In chronic gut diseases, epithelial disruption leads to increased permeability ("leaky gut"), translocation of microbial products, and a sustained inflammatory cascade [4].

Microbiome-driven disease dynamics

Gut microbiota provide critical metabolites—short-chain fatty acids (SCFAs), bile acid derivatives, and tryptophan metabolites—that regulate immune tolerance and stem cell proliferation. Dysbiosis, defined by loss of commensal taxa and expansion of pathobionts, correlates with disease severity in Crohn's disease and ulcerative colitis [5]. For instance:

- Butyrate depletion reduces stem cell proliferation and barrier repair.
- Indole derivatives from tryptophan metabolism modulate the aryl hydrocarbon receptor (AhR), influencing epithelial immunity.

Mitochondrial dysfunction as a convergent mechanism

Mitochondrial health is increasingly recognized as central to gut diseases [6]. In IBD, epithelial mitochondria exhibit reduced oxidative phosphorylation, impaired ATP generation, and excessive ROS production. Similar dysfunction occurs in infiltrating immune cells, sustaining inflammatory activation. Importantly, mitochondrial dysfunction impairs epithelial progenitor cell renewal, linking energy metabolism directly to regenerative failure.

Organ-Specific Precursor and Progenitor Stem Cells for Gut Regeneration

Gastric progenitors and regeneration

Lineage tracing studies have identified isthmal progenitor cells in the stomach as key drivers of mucosal turnover [7]. These progenitors regenerate surface mucous and glandular lineages. Injury models demonstrate that transplantation of gastric organoid-derived progenitors accelerates repair of ulcerated mucosa. Patient-derived gastric organoids also provide a platform for autologous regenerative therapy.

Intestinal crypt progenitors

The intestinal epithelium renews every 4–5 days, driven by **crypt-base columnar LGR5+ stem cells** and progenitor pools [8]. These cells give rise to absorptive enterocytes, goblet cells, and Paneth cells. Organoid technology has enabled long-term expansion of LGR5+ stem cells, which have been transplanted successfully in preclinical models to repair mucosal damage.

Microbiome regulation of stem cell niches

The microbiome profoundly influences stem cell niches. Butyrate, a microbial SCFA, promotes progenitor proliferation by inhibiting histone deacetylases. Indole derivatives regulate Wnt and Notch signaling are critical for crypt renewal. Dysbiosis may therefore compromise stem cell regenerative potential [9].

Peptide-Based Therapeutics for Gut Mucosa

Nano-organo peptides (NOPs)

NOPs are rationally designed short peptides engineered for organelle targeting, receptor binding, or biomimetic functions. Their nanoscale size permits mucosal penetration, while conjugation strategies enhance stability in the GI tract. Preclinical studies demonstrate that NOPs accelerate epithelial migration, stimulate angiogenesis, and modulate immune responses [10].

Mitochondrial-organelle peptides (MO peptides)

MO peptides such as SS-31 (elamipretide) stabilize cardiolipin in mitochondrial membranes, enhance oxidative phosphorylation, and reduce ROS [11]. In models of IBD, mitochondrial peptides restore ATP levels and attenuate epithelial apoptosis. MO peptides may also rescue mitochondrial function in progenitor cells, supporting their regenerative potential.

Peptide–microbiome interactions

The microbiota influence peptide bioavailability by secreting proteases that degrade therapeutic peptides. Conversely, peptide therapies may alter microbial ecology by stimulating host production of antimicrobial peptides (e.g., defensins) or by directly shaping microbial niches [12].

Durable mucosal healing in chronic gut disease necessitates interventions that couple structural regeneration with bioenergetic reprogramming. Stem cell platforms—including intestinal organoid-derived epithelial progenitors and mesenchymal stromal cells (MSCs)—can replenish depleted cell lineages, restore crypt–villus architecture, and secrete trophic factors that dampen inflammation and enhance barrier repair.[1–3] However, the hostile metabolic milieu of chronic gut inflammation—characterized by hypoxia, excessive ROS, and disrupted nutrient flux—limits engraftment efficiency and functional integration.[4–5] Organelle-targeted peptides, particularly MO and NOPs, directly optimize oxidative phosphorylation, stabilize cristae morphology, and activate cytoprotective signaling cascades (e.g., AMPK–PGC1α, mitophagy circuits), thereby enhancing the survival and resilience of both trans-

planted and resident cells.[6–8] Therapeutic platforms increasingly integrate these modalities: **(i) co-delivery systems**, such as bioengineered hydrogels or extracellular-matrix–mimetic scaffolds embedding stem cells with MO peptides, provide localized, sustained metabolic and structural support at mucosal injury sites;[9] [10] **(ii) sequential regimens**, wherein peptides are deployed as niche-preconditioning agents to restore redox and metabolic tone before transplantation, or as post-engraftment adjuvants to boost progenitor integration, barrier restitution, and tolerance signaling.[11] [12] Such dual-pronged strategies exemplify next-generation regenerative therapeutics that move beyond single-modality repair, offering a path toward durable remission in inflammatory bowel disease and related chronic enteropathies.

Recent clinical translation of peptide-based therapies in gut disease highlights their emerging role as both direct therapeutics and adjuncts to regenerative strategies. In steroid-resistant ulcerative colitis, a Phase IIa randomized trial of adrenomedullin (AM) demonstrated significant improvements in Mayo scores and remission rates, supporting its mucosal healing and immunomodulatory potential.[1] Oral peptide antagonists such as PTG-100, targeting the α4β7 integrin, have advanced through Phase 1 and 2a studies in moderate-to-severe ulcerative colitis with evidence of safety, gut-selective activity, and early efficacy, with a larger Phase 2b trial underway.[2] Nutritional peptide formulations have also shown therapeutic benefit: a retrospective study of pregnant women with Crohn's disease reported >80% remission with exclusive peptide-based enteral nutrition, suggesting both efficacy and safety in sensitive populations.[3] Beyond human trials, agents such as glepaglutide (a GLP-2 receptor agonist) demonstrate robust mucosal regenerative and anti-inflammatory activity in preclinical colitis models,[4] while olamkicept (sgp130Fc), though a fusion protein, exemplifies peptide-adjacent targeting of IL-6 trans-signaling with Phase II efficacy in IBD.[5] Collectively, these advances underscore the therapeutic versatility of peptide interventions in restoring barrier integrity, modulating immune–metabolic signaling, and enhancing mucosal resilience in chronic gut disease.

Peptide Therapy	Target / Mechanism	Disease Context	Trial Phase / Findings
Adrenomedullin (AM)	Pleiotropic, mucosal healing	Steroid-resistant UC	Phase IIa; improved Mayo scores & remission signals
PTG-100	α4β7 integrin antagonist	Moderate-to-severe UC	Phase 1/2a completed; Phase 2b underway
Peptide-based formula	Nutritional with peptides	Crohn's disease in pregnancy	Retrospective: 85.7% remission in 12-week protocol
Glepaglutide (GLP-2 agonist)	Epithelial regeneration	Preclinical (rat models)	Strong anti-inflammatory & regenerative efficacy
Olamkicept (sgp130Fc)	IL-6 trans-signaling inhibitor	Active IBD (including UC)	Phase IIa/b: target engagement; some achieved remission

Table 1: Comparison of current vs. emerging therapies for gut diseases.

Convergence at the Epithelial–Microbiome–Mitochondrial Interface.

Integrative therapy can be conceptualized as restoring a tripartite axis that maintains gut homeostasis. First, mitochondrial restoration in intestinal epithelial and stem cells re-establishes oxidative capacity, lowers pathological ROS, and reactives regeneration programs by normalizing fusion–fission dynamics (e.g., OPA1), phospholipid trafficking (e.g., STARD7), and mitochondria–ER Ca^{2+} crosstalk; these pro-

cesses directly couple to epithelial renewal and barrier fitness . In parallel, barrier–microbiome homeostasis is reinforced by boosting tight-junction assembly and energy supply for mucus and antimicrobial peptide (AMP) production, which together spatially confine microbes and stabilize a symbiotic ecology that resists dysbiosis . Finally, immune–metabolic recalibration limits maladaptive inflammasome and NF-κB signaling while promoting tolerance via mitochondrial signaling and microbially derived metabolites (notably SCFAs and tryptophan/aryl hydrocarbon receptor ligands) that reprogram epithelial and myeloid metabolism and sustain Treg circuitry. Collectively, these convergent mechanisms link epithelial bioenergetics to barrier integrity and host–microbe détente, offering tractable therapeutic nodes, from mitochondrial quality control to AMP induction and SCFA augmentation, to restore durable mucosal health .

Together, these synergistic strategies move beyond symptomatic control toward durable, mechanistically grounded mucosal regeneration, positioning stem cell–peptide therapy as a next-generation approach for chronic gastrointestinal diseases.

Translational and Clinical Considerations

Preclinical Models.

Advanced in vitro and in vivo platforms are essential for evaluating integrative stem cell–peptide therapies in a human-relevant context. Organoids and gut-on-chip systems allow mechanistic testing of progenitor–peptide interactions within microbiome-informed microenvironments, capturing epithelial, immune, and microbial crosstalk.[1–3] Murine models of IBD provide valuable insights into inflammatory pathways, engraftment dynamics, and metabolic modulation, though they are limited by differences in microbial composition and immune responses compared with humans.[4–5]

These models have demonstrated that the GI lumen imposes significant barriers, including low pH, proteolytic degradation, and dense mucus layers. Strategies to overcome these challenges include (but are not limited to) nanoparticle encapsulation to protect peptides from degradation and enable controlled release,[6–7] mucoadhesive carriers for enhanced local retention at injured mucosa,[8] and encapsulation of stem/progenitor cells within protective biomaterials such as hydrogels or scaffolds to maintain viability and support engraftment.[9–11]

Biomarkers and Clinical Trial Endpoints.

Comprehensive evaluation of integrative stem cell–peptide therapies in chronic gut diseases requires multi-dimensional, mechanistically informed readouts that capture microbiome, mitochondrial, and clinical outcomes. Microbiome-based metrics assess restoration of SCFA-producing taxa, shifts in microbial composition, functional metabolomic signatures, and biofilm architecture, reflecting the degree of epithelial–microbial homeostasis achieved.[12–13] Mitochondrial health is monitored through bioenergetic indicators, including ATP:ROS ratios, mitochondrial DNA copy number, and oxygen consumption rates, which provide insight into cellular metabolic recovery and regenerative potential.[14–15] Finally, clinical endpoints (e.g., endoscopic evidence of mucosal healing, flare frequency and severity, patient-reported symptom scores, and quality-of-life indices) translate preclinical and mechanistic findings into patient-relevant outcomes.[16] Together, these integrated readouts enable a holistic assessment of therapeutic efficacy, guiding optimization of treatment regimens, validating mechanistic hypotheses, and

informing precision-guided interventions aimed at durable mucosal restoration and long-term functional resilience. By integrating preclinical validation, delivery optimization, and biomarker-driven endpoints, this framework facilitates rational translation of stem cell–peptide therapies from bench to bedside, enabling precision-targeted interventions in chronic gut diseases.

Future Directions and Conclusion

Tailoring stem cell–peptide therapies to an individual's microbiome and metabolome profile can optimize efficacy, reduce adverse responses, and enable endotype-guided interventions for chronic gut diseases.[1–3]

In addition, engineering progenitor cells to exhibit enhanced stress resistance or secrete microbiome-responsive peptides offers the potential to adaptively modulate mucosal environments in situ, improving engraftment and regenerative capacity.[4–5] Complementing these cellular strategies, rationally designed NOPs with programmable organelle-specific functions can restore mitochondrial activity, optimize epithelial metabolism, and suppress inflammatory signaling, thereby synergizing with progenitor-based therapies to enhance mucosal repair and homeostasis.[6–7] Moreover, AI-guided analytics, non-invasive mucosal imaging, and wearable biosensors enable real-time monitoring of therapy outcomes, microbiome shifts, and metabolic responses, supporting dynamic, data-driven adjustments in treatment regimens.[8–10]

Further, tri-modality strategies combining progenitor cells, organelle-targeted peptides, and engineered probiotics can re-establish a fully functional mucosal ecosystem, simultaneously addressing epithelial regeneration, metabolic homeostasis, and microbiome balance.[11–13] These forward-looking strategies envision a mechanistically grounded, precision-guided, and multi-modal therapeutic paradigm for chronic gut diseases, advancing beyond symptomatic control toward durable mucosal restoration and long-term healthspan improvement.

In conclusion, chronic gut diseases arise from failure of the epithelial–microbiome–mitochondrial axis. Therapies that address only inflammation neglect the fundamental deficits in regeneration and energy metabolism. Organ-specific progenitor cells and peptide-based therapeutics represent complementary strategies to restore mucosal integrity and mitochondrial health. Their convergence, supported by advances in organoid biology, peptide engineering, and microbiome science, offers a path to precision regenerative therapies capable of transforming treatment of gastrointestinal diseases.

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