iMASSAGE: Programmable extracellular vesicle therapy for chronic gut disorders and beyond

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Gut microbial homeostasis plays a significant role in the prevention and treatment of various gut diseases. While several interventions, such as probiotics, prebiotics, postbiotics, fecal microbiota transplantation, and dietary recommendations, are already clinically used to modulate the gut microbiome, each has limitations that make them unsuitable as first-line treatments.[1-3]

Recently, extracellular vesicles (EVs) derived from microbes, plants, and mammalian cells have been increasingly recognized as powerful tools for microbiome modulation. These lipid membrane-bound structures are secreted by all cells and act as key mediators of intercellular communication. EVs have demonstrated potential in modulating diverse microbiomes, including those of the skin, gut, vagina, and lungs, positioning them as multifunctional and universal candidates for treating a wide range of conditions.[4-6] They are often considered more effective than whole-cell approaches and may ultimately replace therapies such as fecal microbiota transplantation.

It has already been demonstrated that host cell-derived EVs can reshape gut microbiota composition and restore microbial homeostasis. These EVs carry specific miRNA and protein cargoes, such as bactericidal/permeability-increasing protein and miR-200b-3p, that can impact the proliferation and viability of the bacteria and ultimately restore a diseased gut microbiome to a healthy state.[7,8] Their nanoscale size and human cell origin give EVs superior tissue permeability and bioavailability, enhancing their therapeutic potential. The regulatory effect of EVs is typically sufficient to maintain a healthy gut. However, in disease states such as colitis or inflammatory bowel disease (IBD), the body's natural EV-mediated microbiome regulation often falls short of achieving therapeutic outcomes.

Therefore, the central question is: how can we mobilize the therapeutic power of autologous EVs and stimulate their production *in situ* in a controlled and on-demand manner to effectively modulate the microbiome?

To address this challenge, a recent groundbreaking study published in *Nature Communications* introduced iMASSAGE (inducible mechanical activation for *in situ* and sustainable generation of EVs), a mechanoelectrical implant designed to stimulate the production of autologous EVs in a targeted and controllable manner.[9] This innovation represents a major advance in precision *in situ* EV biosynthesis, paving the way for programmable, patient-specific microbiome therapies. This technology represents a major step forward in translating EVs from physiological mediators of intercellular communication into active, programmable therapeutics, offering a scalable, safe, and personalized solution for microbiome-related diseases.

The iMASSAGE device is an innovative mechanoelectrical platform designed to stimulate on-demand production of autologous EVs within the body to modulate gut microbiota. iMASSAGE employs mechanical stress-sensitive EV-producing host cells embedded in optomechanically responsive hydrogels. These hydrogels contract upon exposure to specific stimuli, applying controlled mechanical forces to the embedded cells. This mechanical stress activates mechanotransduction pathways that drive EV biogenesis and release from the embedded cells within the hydrogel matrix. The released EVs can then act locally to modulate the microbiome, enabling controlled and on-demand therapeutic effects.

iMASSAGE produces EVs by employing host-derived cells – M2 macrophages. Because these cells are involved in immune regulation and microbiome homeostasis, they represent a biologically relevant cell source for generating therapeutic EVs. EVs produced by M2 macrophages substantially increased the number of operational taxonomic units and improved alpha-diversity indices, indicating greater gut microbiota diversity compared to the untreated microbiome. In addition, these EVs significantly increased the abundance of beneficial gut bacteria, such as *Lactobacillus* and *Odoribacter*.[10] They also restore key microbial metabolites to healthy levels, which is essential for maintaining

intestinal function. These findings indicate that EVs produced by iMASSAGE represent a promising therapeutic approach for gut-related diseases.

iMASSAGE is built on two key innovations: a conceptual advance and a technological advance. Conceptually, it enables on-demand, remotely controlled stimulation of EV production *in situ*. Technologically, it employs a mechano-responsive hydrogel that applies precisely controlled mechanical forces to embedded host cells, eliminating the need for drugs, chemicals, or bacteria that could introduce adverse effects. In contrast to previous implant-based approaches that produce EVs statically, where dosing depends solely on the natural production rate of embedded cells, iMASSAGE enables dynamic, on-demand stimulation of EV release.[9] Other EV-releasing strategies, such as EXOtic devices and embedded three-dimensional bioprinting, offer limited flexibility. Their EV output is fixed and cannot be adjusted after implantation. In contrast, iMASSAGE allows real-time control of EV production based on patient response. This dynamic regulation is critical for achieving optimal *in vivo* accumulation and distribution of therapeutic EVs.[4,5]

The competitive advantage of iMASSAGE lies in its ability to wirelessly control the biogenesis of EVs using optomechanical hydrogels. These hydrogels convert remote photothermal signals into mechanical stress, thereby precisely regulating EV production by host M2 macrophages embedded within the hydrogel. By activating the microLED in the iMASSAGE device, the hydrogel undergoes a temperature change (between 37°C and 42°C), which ensures that the device remains stable within the patient's body and the temperature is not high enough to damage the embedded cells. This temperature change results in a significant reduction in the hydrogel's volume (approximately 70%). The embedded macrophage cells are sensitive to mechanical stress, and the stress upregulates the nuclear localization of Yes-associated protein (YAP), which plays a significant role in stimulating EV secretion.[6,11] The study demonstrated that the YAP facilitated the formation of intraluminal multivesicular bodies, which are essential precursors of EV biogenesis. In addition, the presence of YAP also increased the level of proteins that are involved in EV biogenesis. The shrinkage of the hydrogel matrix provides the mechanical stress required to activate and enhance the EV production rate without damaging the embedded cells. Moreover, by comparing the EVs produced from the stimulation of iMASSAGE and static (normal body condition) M2 macrophages, the study also confirmed that mechanical and minor thermal stimulation did not alter the normal therapeutic effect of EVs released from host M2 macrophages.

The study also tested multiple mechanosensitive cell types in which mechanical stimulation can promote nuclear localization of YAP. iMASSAGE demonstrated its versatility in promoting EV biosynthesis across various cell types, indicating that the system has broad generality. Furthermore, the diameter of the iMASSAGE implant is only 5.2 mm; therefore, it can be surgically implanted in the gut area relatively easily to perform localized EV release.

Compared to standard M2 macrophage treatment, iMASSAGE offers several key advantages, including enhanced and on-demand release of therapeutic EVs, sustainable EV release over time, and an overall more promising therapeutic outcome.

The study demonstrated that iMASSAGE can provide enhanced, sustainable, and on-demand modulation of the microbiome. Mechanical stimulation by iMASSAGE increases the biosynthesis of macrophage-derived EVs, which are considered key mediators of microbiome modulation, by up to approximately 20-fold under optimized stimulation conditions.

The efficacy of iMASSAGE in colitis and IBD was evaluated in mice, demonstrating a substantial improvement in gut health compared to the control group. From day 1 to day 10, mice treated with iMASSAGE maintained a physiological body weight approximately 10% higher than untreated controls, bringing their body weight closer to that of healthy mice throughout the 10-day treatment period. In addition, iMASSAGE treatment significantly reduced disease severity, as reflected by the disease activity index (DAI). Specifically, mice treated with iMASSAGE had a DAI score of 0, indicating no apparent disease activity, whereas untreated mice had a DAI score of 3, indicating more severe disease, and mice receiving standard M2 macrophage treatment had a DAI score of 2, indicating moderate disease activity. The implantation of iMASSAGE also resulted in additional positive changes, including increased colon length, fewer inflammation spots in colonic tissues, increased the level of anti-inflammatory cytokine (interleukin-10 [IL-10]), and decreased the levels of pro-inflammatory markers (IL-6, IL-1β, tumor necrosis factor-alpha [TNF-α]).

To evaluate the effect of mechanical or photothermal stimulation on EV functionality, Wan *et al.*[9] assessed their structure, size, concentration, zeta potential, and molecular composition. These analyses confirmed that iMASSAGE did not adversely affect EV functionality, and the vesicles retained key physical and biochemical characteristics comparable to those produced under unstressed conditions. In addition, key proteins, miRNAs, and typical exosomal markers, such as CD9 and CD63, remain unchanged for EVs produced under stress conditions, confirming that iMASSAGE promotes the production of therapeutic EVs without altering their structural and biochemical/molecular profiles. Importantly, the EVs produced by iMASSAGE demonstrated the same therapeutic effect as those produced under normal body conditions.

One of the most significant features of iMASSAGE is its ability to sustainably stimulate and release EVs in large quantities for over 5 days. During this period, EV production can be triggered on demand and remains highly reliable. When mechanical stress is applied, EV output increases more than 20-fold relative to baseline; when the signal is removed, production returns to low levels. This on-demand controllability distinguishes iMASSAGE from existing EV-releasing implant platforms. For example, injectable supramolecular hydrogels based on HPMC-liposome crosslinking can achieve tunable EV release kinetics by varying material formulations, but the release profile is pre-determined at the time of fabrication and cannot

be modulated after administration.[12] Similarly, injectable GelMA-based hydrogel patches enable sustained local EV delivery; however, the long-term retention effect beyond 3 weeks remains untested due to the hydrogel degradation.[13] A common limitation shared by these passive release systems is their characteristic burst-release profile: a disproportionately high EV-release rate occurs during the initial phase (typically the first several days), followed by a progressive decline, often reaching only a fraction of the initial rate by the end of the release period.[12,13] In contrast, iMASSAGE enables real-time, binary switching of EV output, from baseline to maximum production, at any point throughout the treatment duration. This dynamic controllability is essential for personalized therapy, where EV dosing needs to be adapted to fluctuating disease activity and individual patient responses.

While iMASSAGE offers several advantages and shows significant promise, it is not without limitations. First, it shares several inherent challenges associated with EV-based therapeutics. In the context of iMASSAGE, the specificity of EV–microbiome interactions remains poorly defined, as EVs derived from M2 macrophages carry bioactive cargo that may affect both pathogenic and commensal bacteria. In addition, the harsh gut microenvironment may degrade EVs, and even locally delivered EVs may undergo rapid clearance through epithelial turnover, peristalsis, and immune cell uptake, resulting in a short functional half-life. Batch-to-batch variability in EV cargo composition also remains a well-recognized challenge in the broader EV therapeutics field. Other limitations of iMASSAGE include the requirement for surgical implantation and retrieval, concerns regarding overall cost-efficiency, manufacturing complexity, limited understanding of long-term biocompatibility and potential off-target effects, incomplete knowledge of the exact therapeutic mechanism, and the absence of a reliable method for monitoring EV dosage *in vivo*.

More specifically, EV-based therapies share some common challenges. EV bioavailability and retention in target organs vary depending on the properties of the EVs and the method of administration, which makes it harder to maintain the therapeutic dose within the target organ. In addition, batch-to-batch heterogeneity may affect therapeutic consistency across different treatment time points.[14] By providing on-demand and localized release of therapeutic EVs, iMASSAGE offers a method to maintain a consistent and localized EV dosage. However, there are still several limitations that require further study to resolve.

Despite iMASSAGE's relatively small size, it still requires surgical implantation and retrieval, which may reduce patient compliance. Another challenge is cost; iMASSAGE treatment is likely to be more expensive than conventional methods, although no direct cost comparison has been conducted. Future cost-effectiveness analyses should account for long-term health benefits, dosing frequency, clinical outcomes, and ease of use. The manufacturing process is also relatively complex, which could limit accessibility and scalability in clinical settings. Moreover, the study was conducted over only 10 days in the mouse gut, leaving long-term biocompatibility and safety largely unexplored. As a result, the full potential of iMASSAGE and the risk of adverse effects in the human gut remain unknown, which warrants further preclinical and clinical studies.

Although the M2 macrophage EVs produced by iMASSAGE demonstrated substantial therapeutic efficacy in improving microbiome homeostasis in colitis and IBD disease models, the exact mechanism of EVs' therapeutic effects remains unclear, which may pose obstacles to regulatory approval and clinical translation of iMASSAGE. Elucidating the mechanism of action is further complicated by the inherently multi-specific nature of EVs. Unlike conventional therapeutics designed around a single drug–target interaction, EVs simultaneously engage multiple cell types, including macrophages, epithelial cells, and immune effectors, activating distinct and parallel signaling cascades across each.[15] The therapeutic potency of M2 macrophage-derived EVs in iMASSAGE, therefore, likely arises from this multicellular mode of action, a complexity that current reductionist pharmacological frameworks are ill-equipped to fully capture.

The iMASSAGE device can provide localized and controlled release of EVs; however, monitoring EV levels in the gut remains challenging. At present, dose control relies on patient response, which may not change quickly in chronic conditions such as colitis and IBD. This creates a risk of overdosing or underdosing. It is, therefore, essential to develop a reliable EV dose-monitoring strategy. One potential solution is to validate device-specific EV-release profiles before implantation and integrate them with wearable biosensor systems capable of tracking patient symptoms and physiological markers. These systems could provide real-time feedback to adjust EV release when required. Looking ahead, iMASSAGE could evolve into a "smart" implant, a living device with continuous monitoring and adaptive control that responds dynamically to lifestyle, diet, and microbiome disturbances.

Nonetheless, several emerging strategies could help mitigate these practical limitations. The requirement for surgical implantation and retrieval could be substantially reduced by adapting iMASSAGE for delivery through minimally invasive endoscopic procedures. In addition, the development of biodegradable device components could eliminate the need for a retrieval procedure, provided that long-term biocompatibility and safe degradation profiles can be established. Regarding cost-efficiency, while the upfront cost of iMASSAGE is likely higher than that of conventional oral EV administration or passive hydrogel-based systems, the overall cost–benefit analysis should account for several factors: iMASSAGE enables prolonged on-demand EV therapy from a single implantation event, potentially reducing the need for repeated dosing, hospital visits, and treatment failures associated with suboptimal EV bioavailability. Furthermore, as manufacturing technologies for micro-scale mechanoelectrical devices and hydrogel fabrication mature, the unit production cost of iMASSAGE is expected to decrease substantially. Standardized, modular device architectures in which the cell-laden hydrogel component can be prepared separately and loaded into a reusable electronic scaffold could further streamline manufacturing and reduce per-patient costs.

In summary, this study demonstrated the promising potential of the iMASSAGE system to transform the therapeutic approach for chronic gut disorders, particularly colitis and IBD, by enabling localized and controllable delivery of EVs.

This work advances our understanding of cellular mechanical stimulation, particularly the role of YAP signaling in EV biogenesis. The study builds on existing knowledge that mechanical stimuli can enhance EV production and advances it by developing a smart system capable of inducing EV biosynthesis *in situ*.

This implant represents a new paradigm for creating "designer" EVs produced by implanted cells *in situ*. Compared to previous EV-releasing implant models, for example, the EXOtic devices, iMASSAGE offers more treatment flexibility by allowing the rate of EV production to be adjusted based on patients' responses after implantation, which is essential for achieving optimal *in vivo* accumulation and distribution of therapeutic EVs.[16]

This work aims to modulate the gut microbiome, often referred to as the "second brain" due to its profound impact on overall health and disease. The major advantages of iMASSAGE include its ability to restore microbial balance, enhance populations of beneficial bacteria, and reduce inflammatory markers, making it a promising alternative to conventional therapies such as oral EV administration or probiotic therapy.

By utilizing the body's own cells and integrating them into a photothermal-sensitive hydrogel matrix, iMASSAGE introduces a next-generation platform for precise and controllable microbiota modulation. Beyond its application in colitis and IBD, iMASSAGE enables localized and adjustable EV delivery, with mechanical stimulation allowing on-demand EV biogenesis at the target site. These features may support future applications in other diseases in which EV-mediated intercellular communication is therapeutically relevant, including cancer and neurodegenerative disorders.

As the field of electromechanical implants evolves, such innovations may redefine therapeutic strategies for microbiome-associated diseases, offering more adaptable and effective treatment options. However, smart implants such as iMASSAGE still pose challenges related to dosage control, overall safety, device retrieval, and cell reloading. Modern technologies such as wearable sensors and minimally invasive surgical techniques could help mitigate these issues.

Despite this promise, the clinical translation of systems such as iMASSAGE raises important and yet unresolved regulatory questions. Unlike conventional EV therapies, iMASSAGE is a combination construct, incorporating a living cell-seeded implant, a stimuli-responsive biomaterial, and *in situ* EV biogenesis, a complexity that does not fit neatly within existing regulatory frameworks. As has been argued elsewhere, the barriers to translation for EV-based systems are not solely technical but reflect fundamental inadequacies in regulatory frameworks that were designed for conventional single-target medicines and were not conceived to accommodate the inherent biological complexity and multi-specificity of EV-based platforms.[17] Early engagement with agencies (e.g., United States Food and Drug Administration, European Medicines Agency) will be essential to determine the appropriate classification and approval pathway. GMP-grade protocols for cell sourcing, hydrogel fabrication, and device assembly must also be established, alongside validated EV potency assays to ensure batch-to-batch consistency. Furthermore, the clinical translation of systems such as iMASSAGE will require a staged development pathway. In the preclinical phase, long-term evaluation in large-animal models (e.g., porcine colitis) is needed to establish device biocompatibility, EV production stability over weeks to months, and systemic EV biodistribution, extending well beyond the current 10-day murine studies. In parallel, the molecular mechanism by which M2 macrophage-derived EVs modulate the gut microbiome must be elucidated.

Clinically, a first-in-human Phase I trial should target patients with refractory colitis or IBD, with primary endpoints including adverse event profiling, device retention, and preliminary EV pharmacokinetics. Subsequent Phase II trials should evaluate efficacy using clinically validated endpoints such as DAI reduction, endoscopic mucosal healing scores, and gut microbiome diversity metrics. Key challenges along this pathway include the absence of standardized real-time *in vivo* EV dose monitoring, the long-term fate of implanted cells (immune rejection, senescence), and the scalability of autologous cell sourcing. The latter may be addressed in future generations through allogeneic or induced pluripotent stem cell-derived cell sources.

Despite these challenges, modern technologies such as wearable biosensors, minimally invasive delivery techniques, and growing regulatory experience with combination products provide a favorable landscape for clinical realization. Looking ahead, iMASSAGE could evolve into a truly "smart" implant, representing a living therapeutic device with continuous monitoring and adaptive control that responds dynamically to changes in lifestyle, diet, and microbiome status.

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