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Organic Mechanoluminescent Nanoparticles for Deep-Brain Neuromodulation: Physical Mechanisms, Translational Challenges and a Theoretical Framework

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Abstract

Organic mechanoluminescent nanoparticles (MLNPs) have emerged as promising nanoplatforms for wireless deep-brain neuromodulation by converting ultrasound-induced mechanical energy into localized light without implanted optical fibers. This review provides a theoretical perspective on the mechanisms, design principles, biomedical applications, and translational challenges of organic MLNPs. Key mechanisms, including piezoelectric polarization, reactive oxygen species (ROS)-mediated chemiluminescence, and Förster resonance energy transfer (FRET), are discussed together with strategies for improving ultrasound responsiveness and biocompatibility. Current applications in sono-optogenetics, bioimaging, and neuromodulation are critically examined. Major barriers, including limited mechanoluminescence efficiency, biological safety, blood–brain barrier penetration, and manufacturing challenges, are highlighted. Finally, a theoretical framework is proposed to guide the rational design and clinical translation of next-generation organic mechanoluminescent nanoplatforms for precision neuromodulation.

Keywords: *Organic mechanoluminescent nanoparticles; Ultrasound; Deep-brain neuromodulation; Sono-optogenetics; FRET.*

1. Introduction

Neurological disorders, including Parkinson's disease, Alzheimer's disease, epilepsy, depression, and glioblastoma, remain major causes of disability and mortality worldwide (Deisseroth, 2015). Many of these diseases originate in deep brain regions that are difficult to access using conventional therapeutic approaches. Deep-brain stimulation (DBS) and optogenetics have demonstrated remarkable potential for precise neuromodulation; however, both techniques require invasive implantation of electrodes or optical fibers, leading to risks such as tissue damage, inflammation, and limited long-term clinical applicability (Deisseroth, 2015; Chen et al., 2021).

Ultrasound has recently emerged as a promising alternative for wireless neuromodulation owing to its non-ionizing nature, deep tissue penetration, and high spatial precision (Wang et al., 2022; Wang et al., 2023a). Unlike visible light, ultrasound can penetrate the skull and deliver energy to deep brain regions, enabling the development of **sono-optogenetics**, where ultrasound is converted into localized optical signals to activate photosensitive neurons (Wu et al., 2019; Wang et al., 2023b). The effectiveness of this strategy depends on nanomaterials capable of efficiently converting mechanical energy into light.

Among various ultrasound-responsive materials, organic mechanoluminescent nanoparticles (MLNPs) have attracted considerable attention because they combine mechanical responsiveness with excellent biocompatibility. Under ultrasonic stimulation, light emission can be generated through mechanisms such as piezoelectric polarization, reactive oxygen species (ROS)-mediated chemiluminescence, and Förster resonance energy transfer (FRET), while molecular engineering and polymeric design enable tunable emission and multifunctional therapeutic performance (Kim et al., 2019; Wang et al., 2023a).

Despite significant progress, the clinical translation of organic MLNPs remains challenging. Limited mechanistic understanding of ultrasound–material interactions, reduced luminescence efficiency in deep tissues, and concerns regarding nanoparticle stability, biodegradability, biosafety, and scalable manufacturing continue to hinder their practical application (Blackmore et al., 2019; Meng et al., 2021). Furthermore, although previous reviews have discussed mechanoluminescent materials, ultrasound-responsive nanoplatforms, and optogenetics separately, a comprehensive analysis integrating these fields while addressing the underlying physical mechanisms and translational barriers for deep-brain neuromodulation remains lacking.

2. Fundamentals of Organic Mechanoluminescence

Mechanoluminescence (ML) is the phenomenon in which materials emit light in response to external mechanical stimuli such as compression, friction, stretching, bending, impact, or ultrasonic vibration (Kim et al., 2019). Unlike conventional photoluminescence, which requires optical excitation, mechanoluminescent materials directly convert mechanical energy into optical emission through various physical and chemical processes (Wang et al., 2022). Owing to this unique energy conversion mechanism, ML has attracted increasing attention for wireless light generation, particularly in biomedical applications where external optical excitation is difficult to achieve.

Recent advances in nanotechnology have extended this concept to mechanoluminescent nanoparticles (MLNPs), enabling localized light generation in biological environments (Wang et al., 2022; Wang et al., 2023a). Among the available mechanical energy sources, ultrasound has emerged as the most attractive because of its non-ionizing nature, deep tissue penetration, and precise spatial focusing (Meng et al., 2021). During ultrasonic irradiation, cyclic compression and rarefaction generate localized mechanical stress that activates mechanoluminescent nanoparticles (Baker et al., 2001). Depending on the material composition, the absorbed mechanical energy can be converted into light through piezoelectric polarization, mechanochemical reactions, reactive oxygen species (ROS)-mediated chemiluminescence, and Förster resonance energy transfer (FRET) (Wang et al., 2022; Choi et al., 2020).

Organic MLNPs differ significantly from conventional inorganic mechanoluminescent phosphors. While inorganic materials generally depend on crystal defects, trapped charge carriers, and non-centrosymmetric crystal structures, organic systems offer greater molecular flexibility and can be chemically engineered to optimize emission wavelength, quantum efficiency, biodegradability, and biocompatibility (Kim et al., 2019; Wang et al., 2023a). Furthermore, donor–acceptor molecular architectures and polymeric matrices facilitate efficient molecular packing and energy transfer, making organic MLNPs highly attractive for biomedical imaging, neuromodulation, and theranostic applications (Meng et al., 2021).

A major advantage of organic mechanoluminescent systems is their ability to integrate multiple light-generation mechanisms within a single nanoplatform. Under ultrasonic irradiation, cavitation induces localized high temperature and pressure, producing reactive oxygen species such as singlet oxygen and hydroxyl radicals (Choi et al., 2020). These reactive intermediates initiate chemiluminescent reactions that generate electronically excited molecular species. Subsequently, the excitation energy can be transferred to fluorescent acceptors through FRET, producing tunable visible or near-infrared (NIR) emission (Wang et al., 2022; Zhang et al., 2019). This multistep energy conversion pathway enables efficient wireless light generation without direct optical excitation.

For deep-brain applications, emission wavelength is a critical design parameter because biological tissues strongly absorb and scatter visible light. Organic molecular engineering allows precise tuning of the emission spectrum by modifying donor–acceptor structures and fluorophore composition. In particular, NIR-emitting mechanoluminescent systems are highly desirable because light within the biological optical window (650–900 nm) exhibits reduced

tissue absorption and scattering, thereby improving penetration depth and imaging sensitivity (Entradas et al., 2020; Meng et al., 2021).

Despite considerable progress, several challenges remain before organic MLNPs can be translated into clinical neuromodulation. The efficiency of ultrasound-induced light generation is strongly influenced by ultrasound parameters, cavitation dynamics, molecular packing, ROS generation, nanoparticle size, and energy transfer kinetics (Baker et al., 2001; Choi et al., 2020). The complex interplay among these factors limits the overall energy conversion efficiency and highlights the need for a deeper understanding of the underlying physical mechanisms. Therefore, systematic investigation of piezoelectric charge generation, ROS-mediated chemiluminescence, and FRET-assisted emission is essential for the rational design of next-generation mechanoluminescent nanoplatforms for wireless deep-brain neuromodulation.

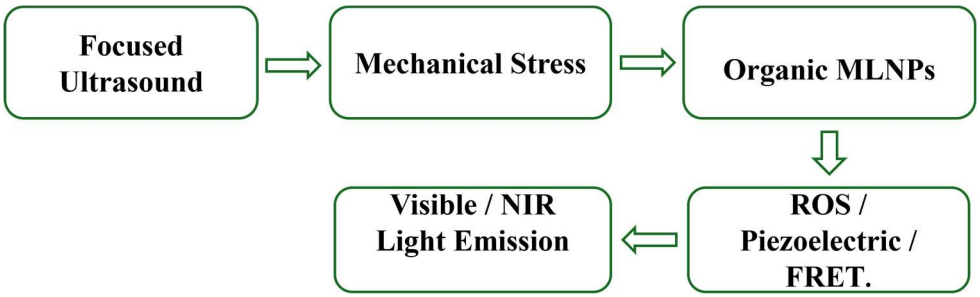

Figure 1. Fundamental mechanisms of ultrasound-induced mechanoluminescence in organic nanoparticles for deep-brain neuromodulation.

3. Design Principles of Organic Mechanoluminescent Nanoparticles for Deep-Brain Neuromodulation

The successful application of organic mechanoluminescent nanoparticles (MLNPs) in deep-brain neuromodulation depends not only on their ability to generate light under ultrasonic stimulation but also on the rational integration of photophysical performance, biological compatibility, and nanoscale engineering (Wang et al., 2022; Wang et al., 2023a). Unlike conventional fluorescent nanoparticles, which rely on continuous optical excitation, organic MLNPs must efficiently convert externally applied mechanical energy into localized optical emission while maintaining structural stability in complex biological environments (Meng et al., 2021; Blackmore et al., 2019). Consequently, the design of organic MLNPs requires the simultaneous optimization of molecular composition, nanoparticle architecture, ultrasound responsiveness, emission characteristics, and biological functionality (Wang et al., 2023a; Li et al., 2016). Recent advances in organic nanotechnology have enabled the development of

multifunctional MLNPs by combining mechanoluminescent molecules, sonosensitizers, fluorescent acceptors, polymeric carriers, and surface-targeting ligands within a single nanoplatform (Wang et al., 2022; Zhang et al., 2019). Each component contributes to the overall performance of the system and directly influences ultrasound-induced light generation, neuronal activation efficiency, and in vivo biosafety (Meng et al., 2021; Gomes et al., 2005). Therefore, material design should be considered a multidisciplinary optimization process rather than the selection of individual luminescent molecules (Blackmore et al., 2019; Baker et al., 2001).

3.1 Organic Mechanoluminescent Luminophores

The mechanoluminescent core is the primary component responsible for converting mechanical energy into optical emission (Kim et al., 2019). In organic systems, mechanoluminescence generally originates from molecular deformation, intermolecular charge transfer, excimer formation, aggregation-induced emission (AIE), or mechanochemical reactions activated by ultrasonic stress (Wang et al., 2022; Kim et al., 2019). Compared with inorganic phosphors, organic luminophores offer several important advantages, including molecular flexibility, tunable emission wavelengths, low intrinsic toxicity, and straightforward chemical modification (Wang et al., 2023a; Meng et al., 2021). Recent molecular engineering strategies have focused on donor–acceptor conjugated systems capable of producing strong visible or near-infrared emission while maintaining high quantum efficiency (Wang et al., 2022; Zhang et al., 2019). Structural modification of aromatic conjugated molecules allows precise control over molecular packing, electronic energy levels, and fluorescence efficiency (Wang et al., 2023a). These properties are particularly important for deep-brain neuromodulation, where sufficient light intensity is required to activate light-sensitive ion channels located several millimeters beneath the skull (Deisseroth, 2015; Chen et al., 2021).

3.2 Sonosensitizers and Ultrasound Responsiveness

Efficient ultrasound-to-light conversion requires materials capable of interacting strongly with ultrasonic energy (Choi et al., 2020; Baker et al., 2001). Sonosensitizers play a central role in this process by enhancing cavitation effects and promoting the generation of reactive oxygen species under ultrasonic irradiation (Choi et al., 2020; Rwei et al., 2017). During acoustic cavitation, the rapid collapse of microbubbles creates localized regions of extremely high temperature and pressure, initiating chemical reactions that produce singlet oxygen, hydroxyl radicals, and superoxide species (Choi et al., 2020; Wang et al., 2018). These reactive intermediates subsequently trigger chemiluminescent reactions or excite nearby fluorophores,

resulting in visible or near-infrared emission (Choi et al., 2020; Pan et al., 2018). The efficiency of this process depends on ultrasound frequency, acoustic intensity, nanoparticle size, and the chemical properties of the sonosensitizer (Baker et al., 2001; Wang et al., 2018). Consequently, the selection of highly efficient and biocompatible sonosensitizers remains one of the most important aspects of organic MLNP design (Choi et al., 2020; Rwei et al., 2017).

3.3 FRET-Based Energy Transfer Systems

Förster resonance energy transfer (FRET) has become one of the most effective approaches for enhancing mechanoluminescent emission in organic nanoparticles (Wang et al., 2022; Zhang et al., 2019). In FRET systems, electronically excited donor molecules transfer energy non-radiatively to nearby acceptor fluorophores through dipole–dipole interactions (Wang et al., 2022). Because this process occurs without photon emission, energy losses are minimized, resulting in higher luminescence efficiency (Zhang et al., 2019). The effectiveness of FRET depends on several factors, including the spectral overlap between donor emission and acceptor absorption, intermolecular distance, molecular orientation, and quantum yield (Wang et al., 2022; Zhang et al., 2019). Careful optimization of these parameters enables wavelength tuning across the visible and near-infrared spectral regions, thereby improving tissue penetration and expanding the range of optogenetic applications (Wang et al., 2022; Meng et al., 2021).

3.4 Polymeric Nanocarriers and Surface Engineering

Organic mechanoluminescent molecules are commonly encapsulated within biodegradable polymeric nanoparticles to improve their stability, dispersibility, and biological compatibility (Wang et al., 2023a; Li et al., 2016). Polymeric matrices protect luminescent molecules from degradation, reduce aggregation-induced quenching, and provide functional groups for further surface modification (Wang et al., 2023a). Surface engineering is equally important for achieving efficient delivery to the brain (Meng et al., 2021; Gomes et al., 2005). Polyethylene glycol (PEG) is widely employed to improve colloidal stability and reduce nonspecific protein adsorption, thereby prolonging blood circulation (Li et al., 2016). In addition, brain-targeting ligands, peptides, antibodies, and receptor-specific molecules can be conjugated to nanoparticle surfaces to facilitate transport across the blood–brain barrier (BBB) and enhance selective accumulation within diseased brain tissues (Meng et al., 2021; Entradas et al., 2020).

3.5 Design Requirements for Clinical Translation

Although considerable progress has been made in improving the optical performance of organic MLNPs, successful clinical translation requires optimization beyond luminescence efficiency alone (Blackmore et al., 2019; Baker et al., 2001). An ideal nanoparticle should simultaneously exhibit high mechanoluminescence intensity, efficient ultrasound responsiveness, strong photostability, nanoscale dimensions, prolonged circulation, low toxicity, controlled biodegradation, and reproducible large-scale synthesis (Meng et al., 2021; Blackmore et al., 2019). These design requirements are closely interconnected (Blackmore et al., 2019). For example, increasing nanoparticle size may enhance luminescence by reducing surface quenching, whereas smaller nanoparticles generally exhibit improved BBB penetration and renal clearance (Meng et al., 2021; Gomes et al., 2005). Similarly, increasing fluorophore concentration may improve emission intensity but can also promote aggregation-induced quenching (Wang et al., 2022; Wang et al., 2023a). Consequently, rational nanoparticle design requires balancing multiple physical, chemical, and biological parameters rather than maximizing a single property (Blackmore et al., 2019; Baker et al., 2001). Future research should therefore focus on integrated nanoplatforms that combine efficient mechanoluminescence, targeted delivery, ultrasound sensitivity, and long-term biosafety within a single multifunctional system (Wang et al., 2022; Meng et al., 2021). Such an approach is expected to accelerate the clinical development of organic MLNPs for wireless neuromodulation and precision neurotherapeutics (Wang et al., 2023a; Blackmore et al., 2019).

Table 1. Representative organic mechanoluminescent nanomaterials and their characteristics for ultrasound-mediated neuromodulation and biomedical applications.

Organic Material	Mechanism	Emission	Biomedical Application	Advantages
AIE luminophores	Molecular deformation	Visible	Bioimaging	High brightness
Donor–Acceptor dyes	Charge transfer	Visible/NIR	Optogenetics	Tunable wavelength
Polymeric MLNPs	ROS-mediated emission	Visible	Neuromodulation	High biocompatibility
FRET nanoplatforms	Energy transfer	Multicolor	Theranostics	High efficiency
Sonosensitizer-loaded nanoparticles	Chemiluminescence	Visible/NIR	Sono-optogenetics	Wireless activation

4. Biomedical Applications of Organic Mechanoluminescent Nanoparticles in Deep-Brain Neuromodulation

The unique ability of organic mechanoluminescent nanoparticles (MLNPs) to convert externally applied ultrasound into localized optical emission has opened new opportunities for wireless neuromodulation and precision medicine (Wang et al., 2022; Wang et al., 2023a). Unlike conventional optical probes that require continuous external illumination, organic MLNPs generate light directly at the target site under ultrasonic stimulation, thereby overcoming the limited penetration depth of visible light and reducing invasive surgical procedures (Chen et al., 2021; Meng et al., 2021). These characteristics have positioned organic MLNPs as promising nanoplatforms for sono-optogenetics, functional brain imaging, and image-guided therapy (Wang et al., 2022; Wu et al., 2019). The biomedical applications of organic MLNPs extend beyond simple light generation (Wang et al., 2023a). By integrating mechanoluminescent molecules, sonosensitizers, fluorescent acceptors, and targeting ligands within a single nanoparticle, these multifunctional systems enable simultaneous diagnosis, therapy, and real-time monitoring (Wang et al., 2022; Zhang et al., 2019). Their ability to produce localized optical signals deep inside biological tissues offers significant advantages for neurological disorders, where precise modulation of neuronal activity is essential (Deisseroth, 2015; Meng et al., 2021).

4.1 Ultrasound-Mediated Sono-Optogenetics

Optogenetics has become one of the most powerful techniques for investigating neuronal circuits because it enables selective activation or inhibition of genetically modified neurons using light-sensitive proteins such as channelrhodopsins, halorhodopsins, and archaerhodopsins (Deisseroth, 2015; Gong et al., 2020). However, conventional optogenetic systems require optical fibers implanted directly into the brain to deliver excitation light, limiting their clinical applicability (Chen et al., 2018; Chen et al., 2021). Organic mechanoluminescent nanoparticles provide an attractive alternative by generating light internally under focused ultrasound irradiation (Wang et al., 2022; Wang et al., 2023a). After systemic or local administration, MLNPs accumulate near genetically modified neurons (Meng et al., 2021). When ultrasound is applied externally, the nanoparticles emit visible light capable of activating nearby opsins without the need for implanted optical devices (Wang et al., 2022; Wu et al., 2019). This wireless strategy significantly reduces tissue damage while preserving the high spatial and temporal precision associated with optogenetic stimulation (Deisseroth, 2015; Chen et al., 2021). Although current ultrasound-induced light intensities remain lower

than those produced by conventional optical fibers, continued improvements in molecular engineering, ultrasound focusing, and mechanoluminescence efficiency are expected to make organic MLNPs increasingly suitable for non-invasive neuronal modulation (Wang et al., 2022; Blackmore et al., 2019).

4.2 Deep-Brain Neuromodulation

Neurological disorders often involve abnormal neuronal activity within deep brain structures that are inaccessible to conventional optical stimulation (Deisseroth, 2015; Fougère et al., 2021). Because ultrasound can penetrate the skull with relatively low attenuation, organic MLNPs have emerged as promising mediators for deep-brain neuromodulation (Meng et al., 2021; Blackmore et al., 2019). In a typical therapeutic process, focused ultrasound propagates through the skull and reaches nanoparticles localized within the target brain region (Meng et al., 2021). Mechanical stimulation activates mechanoluminescent emission, generating localized light that triggers photosensitive ion channels expressed on neuronal membranes (Deisseroth, 2015; Wang et al., 2022). Activation of these ion channels alters neuronal membrane potential, thereby regulating neural circuit activity without direct electrical stimulation (Deisseroth, 2015; Fougère et al., 2021). Compared with deep-brain stimulation (DBS), this approach eliminates implanted electrodes and reduces surgical complications (Won et al., 2020; Salatino et al., 2017). Furthermore, because ultrasound can be accurately focused, neuronal activation can be spatially confined to specific brain regions, minimizing unwanted stimulation of surrounding tissues (Meng et al., 2021; Yu et al., 2021).

4.3 Brain Imaging and Image-Guided Therapy

Organic MLNPs also possess considerable potential as contrast agents for functional brain imaging (Wang et al., 2022; Wang et al., 2023a). Their ultrasound-triggered emission produces exceptionally low background signals because optical excitation is unnecessary, thereby minimizing tissue autofluorescence (Wang et al., 2022). This property enables high-contrast imaging of deep tissues while improving signal-to-noise ratios compared with conventional fluorescent probes (Wang et al., 2023a; Meng et al., 2021). When combined with magnetic resonance imaging (MRI), photoacoustic imaging, or fluorescence imaging, organic MLNPs may provide multimodal imaging capabilities for disease diagnosis and therapeutic monitoring (Hong, 2020; Zhang et al., 2007). Real-time visualization of nanoparticle distribution can further assist clinicians in evaluating treatment efficacy and optimizing ultrasound parameters during neuromodulation procedures (Meng et al., 2021; Blackmore et al., 2019).

4.4 Neurological Disease Therapy

Wireless optical stimulation using organic MLNPs has potential applications in numerous neurological disorders characterized by dysfunctional neuronal circuits (Deisseroth, 2015; Fougère et al., 2021).

Parkinson's Disease

Selective activation of motor-related neuronal pathways using ultrasound-triggered mechanoluminescence may restore functional neural activity while avoiding the complications associated with implanted deep-brain stimulators (Fougère et al., 2021; Won et al., 2020).

Epilepsy

Precise inhibition or activation of epileptic neuronal circuits through ultrasound-mediated optogenetics could suppress seizure activity while minimizing damage to surrounding healthy brain tissues (Deisseroth, 2015; Etter et al., 2019).

Alzheimer's Disease

Targeted neuromodulation may improve neuronal communication, synaptic plasticity, and cognitive function by selectively regulating neural networks involved in memory formation (Etter et al., 2019; Yu et al., 2021).

Depression and Psychiatric Disorders

Wireless modulation of specific neuronal circuits within the limbic system may offer novel therapeutic strategies for treatment-resistant depression and anxiety disorders (Deisseroth, 2015; Etter et al., 2019). Although these applications remain largely in the experimental stage, recent progress in ultrasound-responsive nanomaterials has demonstrated the feasibility of non-invasive optical neuromodulation in animal models (Wang et al., 2022; Wu et al., 2019).

4.5 Theranostic Applications

One of the most attractive characteristics of organic MLNPs is their ability to integrate diagnostic imaging and therapy within a single multifunctional platform (Wang et al., 2022; Wang et al., 2023a). By incorporating therapeutic drugs, photosensitizers, or gene-delivery systems into mechanoluminescent nanoparticles, simultaneous disease diagnosis, targeted drug delivery, and controlled therapeutic activation become possible (Wang et al., 2022; Zhang et al., 2019). Ultrasound serves not only as the external energy source for light generation but also as a trigger for drug release, thereby providing precise spatiotemporal control over therapeutic interventions (Wang et al., 2018; Pan et al., 2018). Such multifunctional nanoplatforms may significantly improve treatment efficacy while reducing systemic side

effects (Wang et al., 2023a; Meng et al., 2021). The overall workflow of ultrasound-mediated deep-brain neuromodulation using organic mechanoluminescent nanoparticles is illustrated in Figure 2.

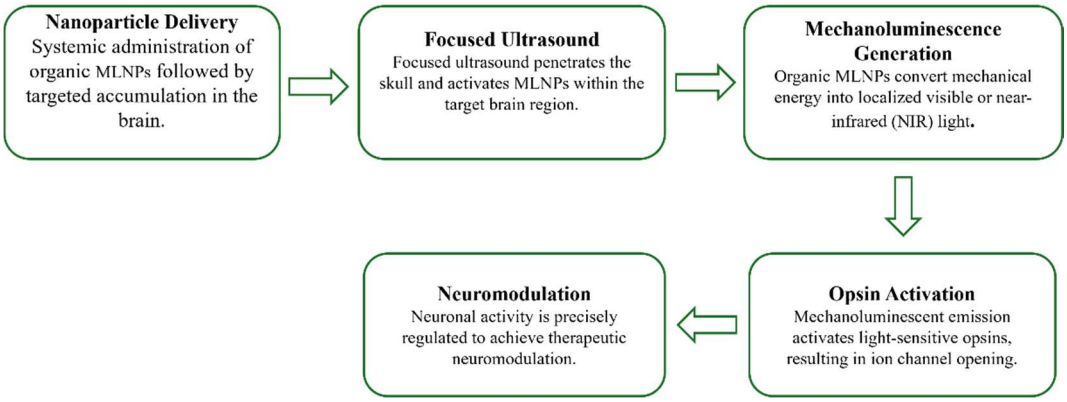

Figure 2. Ultrasound-mediated deep-brain neuromodulation using organic mechanoluminescent nanoparticles.

5. Challenges and Future Perspectives for Clinical Translation

Despite remarkable advances in organic mechanoluminescent nanoparticles (MLNPs), their translation from laboratory research to clinical neuromodulation remains in its infancy (Blackmore et al., 2019; Baker et al., 2001). Most published studies have primarily focused on demonstrating proof-of-concept experiments, whereas comparatively less attention has been devoted to addressing the fundamental physical, biological, engineering, and regulatory challenges required for clinical implementation (Meng et al., 2021; Blackmore et al., 2019). Unlike conventional fluorescent probes, organic MLNPs must simultaneously achieve efficient ultrasound energy conversion, sufficient light intensity for neuronal activation, long-term biological safety, scalable manufacturing, and reproducible performance under physiological conditions (Wang et al., 2022; Blackmore et al., 2019). These requirements are highly interconnected, and optimization of one property frequently compromises another (Blackmore et al., 2019; Baker et al., 2001). Consequently, successful clinical translation requires a multidisciplinary approach that integrates materials science, photophysics, nanotechnology, neuroscience, and biomedical engineering (Meng et al., 2021; Blackmore et al., 2019).

5.1 Physical Limitations of Ultrasound-Induced Mechanoluminescence

The first major challenge concerns the relatively low efficiency of converting mechanical energy into optical emission (Wang et al., 2022; Baker et al., 2001). Although ultrasound penetrates biological tissues much more effectively than visible light, only a small fraction of

the delivered acoustic energy is ultimately transformed into useful luminescence (Blackmore et al., 2019). This limited mechanoluminescence efficiency arises from multiple energy-loss pathways, including acoustic attenuation, cavitation instability, molecular relaxation, non-radiative decay, and inefficient energy transfer between mechanoluminescent components (Choi et al., 2020; Baker et al., 2001). Furthermore, ultrasound propagation itself is influenced by tissue heterogeneity, skull thickness, acoustic scattering, and attenuation (Meng et al., 2021; Blackmore et al., 2019). Variations in acoustic pressure distribution may produce non-uniform nanoparticle activation, reducing stimulation precision within deep brain structures (Baker et al., 2001; Yu et al., 2021). Since neuronal activation requires sufficient local photon density, improving ultrasound-to-light conversion efficiency remains one of the most important research priorities (Wang et al., 2022; Blackmore et al., 2019). Future studies should therefore focus on optimizing molecular structures, ultrasound-responsive nanocomposites, and energy transfer pathways capable of maximizing mechanoluminescent emission under clinically acceptable ultrasound intensities (Wang et al., 2022; Zhang et al., 2019).

5.2 Material Stability and Photophysical Challenges

The long-term performance of organic MLNPs depends strongly on their structural and photophysical stability (Wang et al., 2022; Wang et al., 2023a). Organic luminophores may undergo chemical degradation, molecular rearrangement, fluorescence quenching, or oxidation after repeated ultrasonic stimulation (Blackmore et al., 2019; Baker et al., 2001). These degradation processes gradually reduce emission intensity and limit repeated therapeutic applications (Wang et al., 2022). Aggregation-induced quenching represents another important limitation (Wang et al., 2022; Wang et al., 2023a). Although increasing fluorophore concentration generally improves light generation, excessive molecular aggregation often promotes non-radiative energy dissipation, thereby decreasing luminescence efficiency (Wang et al., 2022). Conversely, reducing fluorophore concentration improves molecular dispersion but frequently results in insufficient photon generation for optogenetic activation (Wang et al., 2022; Zhang et al., 2019). Balancing molecular packing, fluorescence efficiency, mechanical sensitivity, and structural stability therefore remains a central challenge in the rational design of organic mechanoluminescent nanoplatforms (Blackmore et al., 2019; Baker et al., 2001).

5.3 Biological Barriers and Biosafety

Even when sufficient mechanoluminescence is achieved, successful clinical application depends on favorable biological behavior following administration (Meng et al., 2021; Gomes et al., 2005). After entering the bloodstream, nanoparticles rapidly interact with plasma

proteins, forming a protein corona that alters their physicochemical properties and biological identity (Soenen et al., 2011; Dobrovolskaia et al., 2008). This process influences circulation time, cellular uptake, biodistribution, and immune recognition (Soenen et al., 2011; Tsoi et al., 2016). The blood–brain barrier (BBB) represents one of the greatest biological obstacles to deep-brain neuromodulation (Meng et al., 2021; Gomes et al., 2005). Although several targeting strategies have been proposed, efficient and reproducible transport of organic MLNPs into specific brain regions remains difficult (Meng et al., 2021; Entradas et al., 2020). Nanoparticle size, surface charge, hydrophilicity, and ligand density all influence BBB permeability and tissue accumulation (Meng et al., 2021; Gomes et al., 2005). Long-term toxicity also remains insufficiently understood (Bobo et al., 2016; Soenen et al., 2011). Potential accumulation in the liver, spleen, kidneys, and brain raises concerns regarding chronic inflammation, oxidative stress, metabolic clearance, and long-term biodegradation (Soenen et al., 2011; Tsoi et al., 2016). Comprehensive pharmacokinetic and toxicological investigations are therefore essential before clinical translation can be realistically considered (Bobo et al., 2016; Amin and Dannenfelser, 2006).

5.4 Engineering and Clinical Translation Challenges

In addition to physical and biological limitations, several engineering challenges continue to hinder clinical implementation (Blackmore et al., 2019; Baker et al., 2001). Most currently reported organic MLNPs are synthesized at laboratory scale using complex multistep procedures that are difficult to reproduce under industrial manufacturing conditions (Blackmore et al., 2019). Batch-to-batch variation in nanoparticle size, luminescence efficiency, molecular composition, and surface chemistry may significantly affect therapeutic performance (Blackmore et al., 2019; Baker et al., 2001). Standardization of ultrasound parameters represents another unresolved issue (Meng et al., 2021; Baker et al., 2001). Different studies employ varying ultrasound frequencies, acoustic pressures, pulse durations, and exposure times, making direct comparison between experimental systems difficult (Blackmore et al., 2019; Baker et al., 2001). The absence of standardized testing protocols further complicates optimization and regulatory evaluation (Blackmore et al., 2019; Bobo et al., 2016). From a clinical perspective, regulatory approval will require comprehensive characterization of nanoparticle composition, manufacturing reproducibility, long-term stability, biodistribution, biodegradability, immunogenicity, and patient safety (Bobo et al., 2016; Amin and Dannenfelser, 2006). Establishing internationally accepted quality-control guidelines will therefore be essential for future commercialization (Bobo et al., 2016).

5.5 Future Perspectives

Despite these challenges, the future of organic mechanoluminescent nanoparticles remains highly promising (Wang et al., 2022; Wang et al., 2023a). Continued advances in molecular engineering, supramolecular chemistry, biodegradable polymers, ultrasound physics, artificial intelligence-assisted materials design, and precision nanomedicine are expected to accelerate the development of next-generation wireless neuromodulation platforms (Wang et al., 2022; Meng et al., 2021). Future research should shift from optimizing isolated material properties toward integrated multifunctional systems capable of combining efficient mechanoluminescence, targeted brain delivery, multimodal imaging, controlled drug release, and long-term biological safety within a single nanoplatform (Wang et al., 2022; Zhang et al., 2019). Such systems may enable personalized neuromodulation therapies with improved precision and minimal invasiveness (Wang et al., 2023a; Meng et al., 2021).

Table 2. Major challenges limiting the clinical translation of organic mechanoluminescent nanoparticles and potential strategies for future development.

Challenge	Scientific Basis	Current Limitation	Future Strategy
Low mechanoluminescence efficiency	Poor ultrasound-to-light conversion	Weak neuronal stimulation	Molecular engineering & optimized FRET
Material instability	Molecular degradation & quenching	Reduced emission after repeated stimulation	Stable polymeric architectures
Blood–brain barrier	Limited nanoparticle transport	Poor brain accumulation	Targeted ligands & biomimetic coatings
Long-term biosafety	Unknown biodegradation & clearance	Clinical uncertainty	Biodegradable organic nanomaterials
Manufacturing reproducibility	Batch variation	Regulatory limitations	Standardized synthesis protocols
Regulatory approval	Lack of clinical guidelines	Delayed commercialization	International quality-control standards

6. A Theoretical Framework for the Clinical Translation of Organic Mechanoluminescent Nanoparticles

The preceding sections demonstrate that the successful development of organic mechanoluminescent nanoparticles (MLNPs) for deep-brain neuromodulation is governed by

multiple interdependent factors rather than a single material property (Wang et al., 2022; Blackmore et al., 2019). Although considerable progress has been achieved in improving molecular design, ultrasound responsiveness, and mechanoluminescence efficiency, these individual advances alone are insufficient to ensure successful clinical translation (Meng et al., 2021; Blackmore et al., 2019). Instead, future development requires a comprehensive strategy that integrates material engineering, photophysical performance, biological compatibility, and translational feasibility into a unified design philosophy (Wang et al., 2022; Meng et al., 2021). Based on the critical analysis presented throughout this review, we propose a theoretical framework describing the sequential pathway for the clinical translation of organic mechanoluminescent nanoparticles (Wang et al., 2022; Blackmore et al., 2019). Unlike conventional material-centered approaches, this framework considers clinical implementation as a multidisciplinary optimization process in which each stage directly influences the performance of the subsequent stage (Meng et al., 2021; Blackmore et al., 2019). The proposed model consists of six interconnected components: material design, ultrasound–material coupling, mechanoluminescence generation, neuron–light interaction, biological compatibility, and clinical translation (Wang et al., 2022; Wang et al., 2023a).

The first stage involves rational material design, which establishes the physicochemical foundation of the nanoparticle system (Wang et al., 2022; Kim et al., 2019). Selection of organic luminophores, sonosensitizers, donor–acceptor fluorophores, biodegradable polymer matrices, and surface functionalization determines the optical characteristics, mechanical responsiveness, nanoparticle stability, and biological properties of the final nanoplatform (Wang et al., 2022; Zhang et al., 2019). Careful molecular engineering at this stage governs not only luminescence efficiency but also circulation stability, biodegradability, and targeting capability (Wang et al., 2023a; Li et al., 2016). The second stage focuses on ultrasound–material coupling, where externally applied ultrasound interacts with the nanoparticle to generate localized mechanical stress (Choi et al., 2020; Baker et al., 2001). The efficiency of this process depends on ultrasound frequency, acoustic pressure, cavitation dynamics, molecular deformation, and the intrinsic mechanical sensitivity of the organic material (Choi et al., 2020; Baker et al., 2001). Efficient coupling maximizes mechanical energy transfer while minimizing unnecessary tissue heating and energy loss (Meng et al., 2021; Blackmore et al., 2019). The third stage is mechanoluminescence generation, representing the central functional process of the nanoparticle (Wang et al., 2022; Choi et al., 2020). Mechanical stimulation activates piezoelectric polarization, sonochemical cavitation, reactive oxygen species (ROS)-

mediated chemiluminescence, and Förster resonance energy transfer (FRET), ultimately producing localized visible or near-infrared emission (Wang et al., 2022; Choi et al., 2020; Zhang et al., 2019). The intensity, wavelength, and duration of emitted light determine the effectiveness of subsequent neuronal stimulation (Deisseroth, 2015; Wang et al., 2022). The fourth stage involves light–neuron interaction, where ultrasound-generated photons activate genetically encoded light-sensitive ion channels such as channelrhodopsins expressed on neuronal membranes (Deisseroth, 2015; Gong et al., 2020). This interaction regulates ion transport across the cell membrane, modifies neuronal membrane potential, and ultimately modulates neural circuit activity (Deisseroth, 2015; Fougère et al., 2021). The efficiency of neuronal activation depends on emission wavelength, photon density, nanoparticle localization, and the expression level of optogenetic proteins within the target tissue (Deisseroth, 2015; Chen et al., 2021). The fifth stage addresses biological compatibility, which determines whether the nanoplatform can function safely within the physiological environment (Meng et al., 2021; Gomes et al., 2005).

Following systemic administration, nanoparticles must exhibit favorable biodistribution, efficient transport across the blood–brain barrier, minimal immune recognition, controlled biodegradation, and acceptable long-term biosafety (Soenen et al., 2011; Tsoi et al., 2016). These biological factors directly influence therapeutic efficacy and remain essential prerequisites for future clinical application (Bobo et al., 2016; Soenen et al., 2011). The final stage is clinical translation, where all previous requirements must be simultaneously satisfied (Blackmore et al., 2019; Baker et al., 2001). Successful implementation requires reproducible large-scale synthesis, standardized ultrasound protocols, manufacturing consistency, regulatory approval, and demonstrated long-term safety and therapeutic effectiveness (Bobo et al., 2016; Amin and Dannenfelser, 2006). Failure to optimize any individual stage may significantly reduce overall clinical performance, regardless of improvements achieved in other components of the system (Blackmore et al., 2019; Baker et al., 2001). The proposed framework emphasizes an important conceptual shift in the development of organic mechanoluminescent nanoparticles (Wang et al., 2022; Meng et al., 2021).

Rather than maximizing individual material properties, future investigations should prioritize balanced optimization across the entire translational pathway (Wang et al., 2022; Blackmore et al., 2019). Integrating material science, ultrasound physics, molecular photophysics, neuroscience, nanomedicine, and biomedical engineering into a single development strategy is expected to accelerate the realization of clinically viable wireless neuromodulation

technologies (Wang et al., 2022; Meng et al., 2021). Although this framework is theoretical, it provides a rational roadmap for future interdisciplinary research (Wang et al., 2022; Wang et al., 2023a). By identifying the critical relationships between material design, mechanoluminescence generation, neuronal activation, biological safety, and clinical implementation, it establishes a conceptual foundation for the next generation of organic mechanoluminescent nanoplatforms designed for precision neuromodulation and translational neuroscience (Wang et al., 2022; Meng et al., 2021). The proposed theoretical framework for the clinical translation of organic mechanoluminescent nanoparticles is summarized in Figure 3.

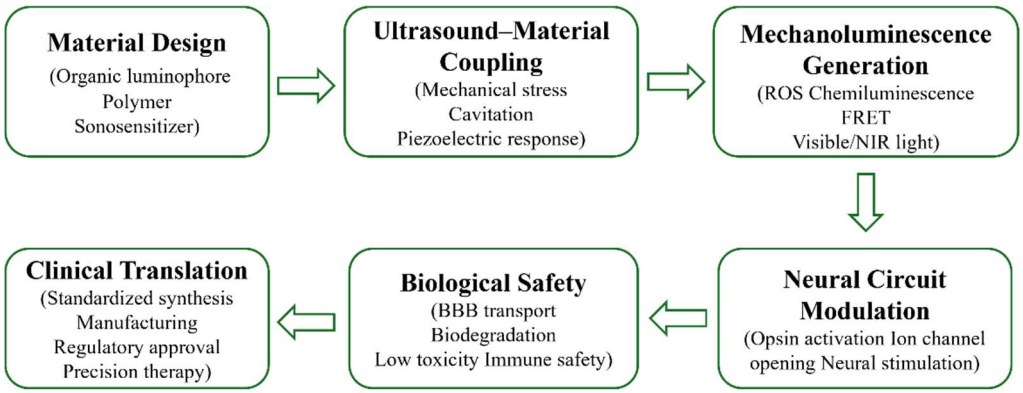

Figure 3. Integrated theoretical framework linking material design, mechanoluminescence, biological compatibility, and clinical translation of organic MLNPs.

7. Conclusions

Organic mechanoluminescent nanoparticles (MLNPs) represent a promising platform for wireless deep-brain neuromodulation by converting ultrasound into localized light without implanted optical fibers. Their unique ultrasound responsiveness, tunable optical properties, and biocompatibility offer significant potential for sono-optogenetics, bioimaging, and precision neurotherapeutics. However, challenges including limited mechanoluminescence efficiency, incomplete understanding of ultrasound–material interactions, blood–brain barrier penetration, long-term biosafety, and scalable manufacturing continue to hinder clinical translation. This review provides a theoretical perspective on the fundamental mechanisms, material design, biomedical applications, and translational challenges of organic MLNPs. Furthermore, the proposed theoretical framework offers a systematic roadmap for integrating material design, mechanoluminescence, biological compatibility, and clinical translation. Continued interdisciplinary research in materials science, nanotechnology, ultrasound engineering, and neuroscience will be essential for developing next-generation organic mechanoluminescent nanoplatforms for non-invasive precision neuromodulation.

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