Commentary

Attaching Nanomaterials to the Cell Surface for Better Performance

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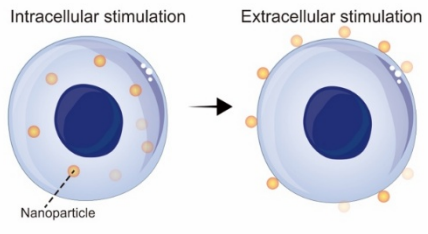
Received: 6 December 2025; Accepted: 15 December 2025; Published:17 December 2025

Abstract: Piezoelectric nanostickers offer a promising strategy for neuronal repair by shifting stimulation from inside the cell to the cell surface and thereby overcoming lysosomal sequestration and potential cytotoxicity. This article highlights the mechanism, therapeutic potential, and key challenges toward clinical translation of this extracellular approach.



Keywords: nanomaterials; cellular internalization; cell surface

It is a major clinical challenge to repair traumatic brain injury (TBI), which is characterized by rapid neurological decay and long-term functional deficits [1]. The inherent difficulty stems from the limited regenerative potential of the central nervous system in adults. Neural stem cells (NSCs) offer a potential solution owing to their ability to differentiate into neurons or glial cells, but, in the absence of instructive cues, their spontaneous differentiation remains slow, inefficient, and often diverted from the neuronal lineage [2]. To this end, it is of paramount importance to develop effective strategies capable of regulating the fate of NSCs and accelerating neuronal differentiation. Recent years have witnessed the successful development of functional nanomaterials with well-controlled properties to guide the differentiation of NSCs toward neuronal lineages. In general, these nanomaterials exert their roles by interacting with the cells through either intracellular or extracellular stimulation.

In the case of intracellular stimulation, the nanomaterials are internalized by the cells prior to exerting their roles in the cytoplasm or specific organelles. Although this strategy may appear to be straightforward, its practical use is hampered by major biocompatibility issues, particularly for piezoelectric nanomaterials that have been shown with high cytotoxicity upon internalization. A notable example involves the use of barium titanate (BTO) nanoparticles [3]. Although BTO nanoparticles exhibit piezoelectric properties suitable for promoting neuronal differentiation, their internalization by cells paradoxically induces cytotoxic effects and compromises cell viability. The key issue lies in how BTO nanoparticles are processed inside the cell: once internalized, they are typically sequestered in the acidic environment of lysosomes. When subjected to ultrasound (US) irradiation to produce piezoelectric stimulation, this acidic sequestration can trigger a deleterious oxygen-evolution reaction, leading to the uncontrolled generation of highly reactive oxygen species. As a result, intracellular delivery is a detrimental strategy for this class of piezoelectric nanomaterials.

The extracellular route, in contrast, relies on nanomaterials capable of anchoring to the cell membrane for the delivery of factors directly to surface receptors or ion channels. Writing in *Nature Materials*, Qiu and coworkers report an elegant solution that moves the focus of stimulation from inside the cell to the cell surface [4]. The authors developed piezoelectric nanostickers comprised of BTO nanoparticles immobilized on flexible, conductive reduced graphene oxide (rGO) nanosheets (Figure 1A). The rGO nanoshet is instrumental in achieving stable adhesion to the cell membrane while preventing the nanoparticles from internalization. The BTO nanoparticles can generate piezoelectric stimulation under US, accelerating neuronal differentiation (Figure 1B,C). When NSCs equipped with these piezoelectric nanostickers were transplanted into the TBI site and exposed to 5-min US sessions every two days for 28 days, the treated tissue showed significant neuronal functional recovery and substantial structural repair (Figure 1D). Taken together, by shifting the location of BTO nanoparticles from the cytoplasm to the cell surface, this work demonstrates an effective method to overcome the critical barrier of

lysosomal sequestration and the subsequent toxicity from highly reactive oxygen species. In addition to BTO-based piezoelectric nanoparticles, other membrane-anchoring strategies have also been developed in the fields of drug delivery and immunotherapy, including Janus particles and microdisks with high biocompatibility [5,6]. These versatile platforms could, in principle, be adapted to anchor to the membrane of NSCs, activating specific surface receptors to promote neuronal differentiation and thereby offering alternative or complementary routes to neuronal regeneration.

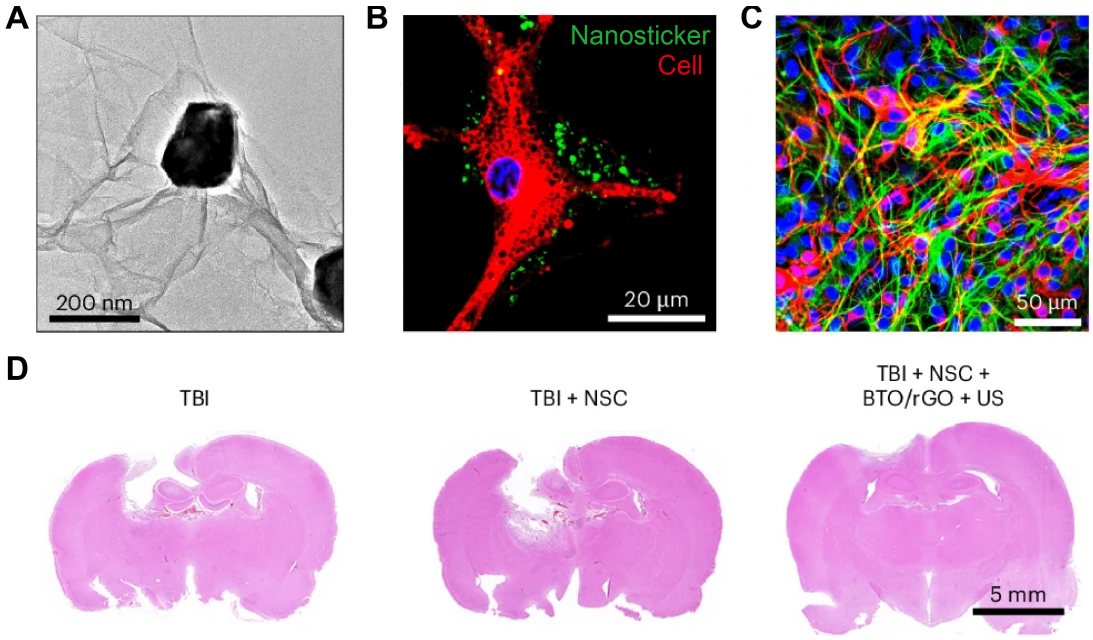


Figure 1. Characterizations and functionality of nanostickers. (**A**) Transmission electron microscopy image of a BTO/rGO nanosticker. (**B**) Fluorescence images showing the spatial distribution of nanostickers (green) on the membrane of NSC (red). (**C**) Fluorescence micrograph showing neurons (red) differentiated from NSCs upon piezoelectric stimulation with US for 15 days. (**D**) Hematoxylin and eosin staining images illustrating enhanced brain tissue regeneration at the TBI site following transplantation of NSCs with BTO/rGO piezoelectric nanostickers and subsequent US irradiation. Modified from Ref. [4] with permission. Copyright 2025, The Author(s).

Moving forward, translating this nanosticker technology from the laboratory to clinical use requires the addressing of several key challenges: (i) Are nanostickers safe and degradable in the brain? While the technology successfully avoids intracellular BTO toxicity, the long-term safety index (e.g., inflammatory response and biodegradability) in the sensitive brain microenvironment remains to be determined. (ii) How to appropriately administer the US stimulation to a patient? Since the therapeutic efficacy of the nanostickers depends on sustained US activation, establishing clinically safe and effective US delivery protocols becomes critical. Key parameters, including the application mode, treatment duration, frequency, and distance to the injury site, all need to be systematically optimized to achieve reproducible piezoelectric stimulation in the patient. (iii) How to achieve standardization and scalability? Transitioning toward large-scale clinical trials requires not only cost-effective and reproducible fabrication of nanostickers but also the establishment of standardized protocols for quality control, safety testing, and performance validation. Such efforts are critical to ensure inter-batch consistency and regulatory compliance during clinical manufacturing. (iv) Can precise control over neuronal lineage be achieved? Different injury models, such as TBI versus spinal cord injury, require distinct neuronal subtypes (e.g., glutamatergic or GABAergic neurons) for proper circuit repair. Achieving such lineage-specific control remains a major challenge in neural tissue engineering. Although the nanosticker can promote neuronal differentiation, further advances are needed to program the fate of NSCs with single-lineage precision, enabling the production of defined neuronal subtypes and supportive glial populations. Overcoming these barriers will be key to translating this nanosticker technology from a proof-of-concept to a clinically viable therapeutic platform.

Funding: This research received no external funding.

Data Availability Statement: Not applicable.

Conflicts of Interest: The author declares no conflict of interest.

Use of AI and AI-assisted Technologies: No AI tools were utilized for this paper.

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