material which I think adds a new dimension to the impact of the research. It can be expected in the future that evaluating the sustainability of materials will become a standard, in addition to the common characterization of density, stiffness, and similar properties.

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Molecular engineering of nanoactuators for neuromodulation

Geumbee Lee[1,2] and John A. Rogers[1,2,3,*]

Some of the most advanced techniques for deep-brain stimulation rely on chronic brain implants that can damage fragile tissues and induce adverse immune responses. Herein, researchers report a macromolecular construct as an injectable photothermal nanotransducer for neuromodulation that bypasses these limitations.

The prevalence of degenerative brain diseases is increasing with the expanding size of the elderly population. The resulting conditions range from movement-related disorders (e.g., essential tremor, dystonia, Parkinson's, Lou Gehrig's, and Huntington's disease) to impaired cognition and/or memory (e.g., Alzheimer's disease, dementia).[1] Treatments rely on medications and physical therapy to control symptoms such as hand tremors and muscle stiffness. Most pharmacological interventions lose their efficacy over time, often with unexpected side effects and health complications. Engineering alternatives based on stimulation of the brain provide attractive alternatives via programmed activation and/or inhibition of pathological signals.

Such forms of deep-brain neuromodulation typically engage with the base of the brain to induce normal patterns of behavior in neural circuits associated with sensory dysfunction.[2] Electrical,[3] optical,[4] thermal,[5] and magnetic[6] modes of operation are available for these purposes, each with advantages and disadvantages. Practical limitations, however, follow from requirements for implanted stimulators (electrical, optical, thermal) or for large resonant coils in close vicinity to the head (magnetic). Associated externalized and/or implanted hardware constrains patient mobility and imposes additional health risks. Permanent damage to the brain can occur during surgical insertion and immune responses can be triggered at any time postoperatively. Although highly miniaturized, wireless platforms as optogenetic interfaces are emerging from laboratory research,[4] an aspirational goal is to eliminate the need for conventional device implants entirely.

A team of researchers at Stanford, led by Prof. Guasong Hong, report an important advance for this area of research in the form of an injectable material for deep-brain stimulation. Their key contribution is in the development of a macromolecular nanotransducer that generates heat when irradiated by light with a wavelength within the second near-infrared spectral window (NIR-II) for transmission through biological tissues.[7] Operation in this regime, specifically at a wavelength of 1,064 nm, minimizes scattering and absorption by water as light passes through brain tissue, thereby enabling excellent penetration and effective operation in the deep brain. These chemical systems consist of organic nanoparticles (~40 nm in average diameter) with a π-conjugated semiconducting polymer

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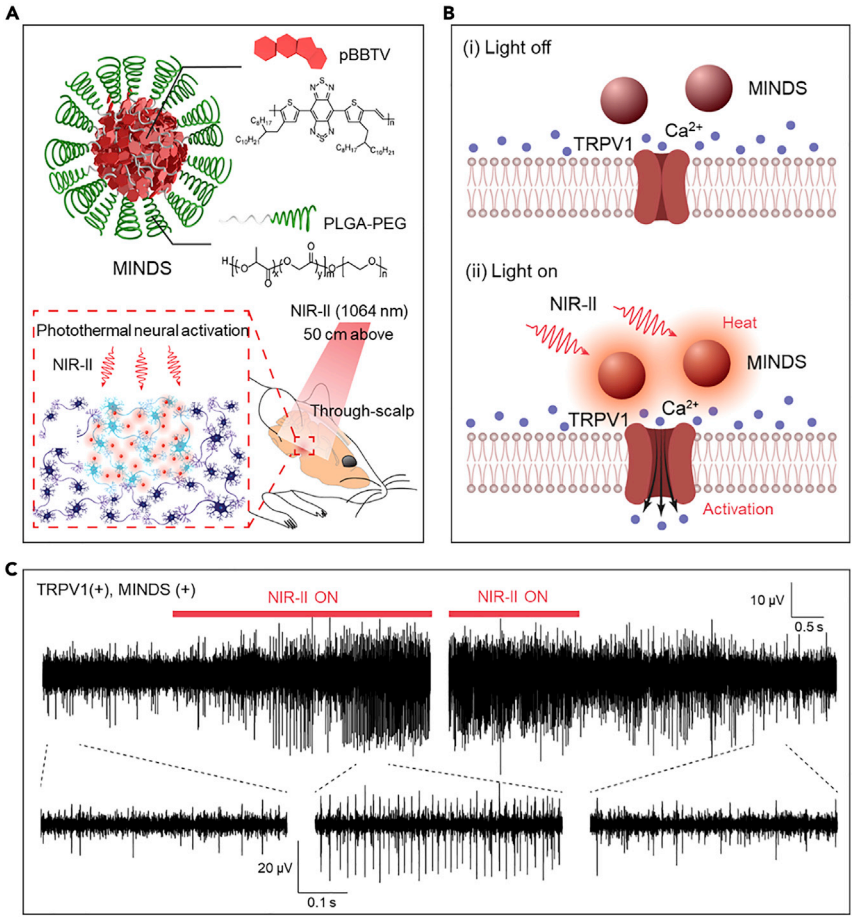

Figure 1. Macromolecular nanotransducers for photothermal control of neural processes

(A) Materials and molecular structure of the nanotransducers (top), and a schematic illustration showing deep-brain stimulation with NIR-II illumination (bottom).

(B) Photothermal activation mechanism enabled by these nanotransducers.

(C) Measured changes in neuron firing rates under NIR-II illumination.

core (poly(benzobisthiadiazole-alt-vinylene)) as an efficient absorber of NIR-II light and an amphiphilic polymer shell (poly(lactide-co-glycolide)-b-poly(-ethylene glycol)) as a biocompatible interface that is water soluble (Figure 1A, top) and also biodegradable.[8] This interesting type of optical-to-thermal nanotransducer can be injected directly into targeted regions of the deep brain as a minimally invasive, materials-oriented alternative to traditional approaches to neuromodulation that rely on implanted device hardware.

Light delivered to the surface of the skull at a distance of 50 cm or more activates these implanted nanotransducers at depths of up to 6 mm. Absorption results in a local heating to actuate temperature-sensitive neural receptors (Figure 1A, bottom) that function as non-selective channels with high permeability to calcium (Figure 1B). Opening these channels increases the firing rate of affected neurons (Figure 1C). Through *in vivo* demonstration experiments, the research team reports that this activation leads to unilateral circling behavior and specific place preference in freely behaving subjects. Systematic studies reveal several attractive features of this process, including rapid response times (<1 s), high optical-to-thermal power conversion efficiencies (71%), and excellent photostability (no degradation over >70 heating/cooling cycles) under physiological conditions.

This photothermal mechanism for neuromodulation has broad potential for neuroscience research, with capabilities that complement those of well-established optogenetic and chemogenetic approaches. Relative to optogenetics, the scheme eliminates requirements for chronic brain implants; relative to chemogenetics, precise temporal control for neural activation and/or inactivation can be achieved easily. One specific consequence is in the ability to dissect complex neural activity of animals, without constraint and in social interacting groups, in a manner compatible with naturalistic experimental arenas. Opportunities for further improvements are in the addition of sensors to enable real-time feedback control of the temperature, potentially enabled by lightweight, fully implantable wireless devices capable of operation continuously in a battery-free mode.[9,10]

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Programmable multicellular and spatially patterned organoids: A one-pot strategy

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The simultaneous differentiation of human-induced pluripotent stem cells (hiPSCs) into different cell types is the basis for obtaining organoids and tissues with complex cell components, structures, and functions. Lewis and colleagues' latest work published in Nature Biomedical Engineering presented a new one-pot orthogonally differentiation strategy combined with a multi-material 3D bioprinting method to generate programmatic patterned organoids and bioprinted tissues. This approach will provide a new roadmap to developing engineered tissues for extensive biomedical applications.

Much of our knowledge of organogenesis, disease development, and tissue repair results from research on model biology such as organoids.[1] Organoids hold great potential for translating basic science into clinical research. Self-assembly and differentiation of embryoid bodies (EBs) formed by the aggregation of human-induced pluripotent stem cells (hiPSCs) and heterogeneous stem cell-derived tissues produced by multi-material 3D bioprinting provide a new scheme for drug screening, disease modeling, and therapeutic applications.[2] However, prolonged differentiation time, low efficiency, poor reproducibility, and limited differentiation scale are the main bottlenecks yet to be solved to fulfill in organoid technologies. Given the existing challenges that these techniques have failed to break through, Lewis and colleagues put forward an innovative strategy that can quickly generate patterned organoids and bioprinted tissues through co-differentiating pre-programmed hiPSCs in a culture-media composition independent manner with near-unity efficiency combined by multi-material bioprinting just within days.[3]

Culture medium-drive extracellular induction cues or intracellular modulation via overexpression of transcription factors (TFs) are the conventional ways to induce hiPSCs in the past years. Human tissues, however, are patterned structures formed by the hierarchical distribution of multiple cell types. Nevertheless, it takes weeks, even months, to achieve cell diversity at the organ level.[4] Just as the gears of history have never stopped, science is still making great strides with the persistent efforts of worldwide scholars. One such progress is human genome screening for specific TFs that can achieve rapid differentiation of hiPSCs once overexpressed.[5,6] Lewis's team sees an opportunity in this advance and induced pre-programmed hiPSCs into specific cell types of interest by TFs overexpression. For example, they generated inducible endothelial (iEndo) cells and inducible neurons (iNeuron) by specifically overexpression of ETV2 and NGN1 TFs, and then orthogonally induced wild type hiPSCs, iEndo, and iNeuron simultaneously by in a one-pot system into neural stem cells, endothelium, and neurons just within days (Figure 1).

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