Adapting Muscle Stimulation Electrodes to Intracranial Applications via Biodegradable Neuroprotective Coatings

RESEARCH STRATEGY

A. SIGNIFICANCE

A1. Chronic neuroinflammation is the principal barrier in adapting peripheral stimulation electrodes for brain applications

Within the past 20 years, functional electrical stimulation (FES) has become a formidable tool in restoring motor function to spinal cord injury patients through direct activation of peripheral muscles' motor axons. Using these peripheral electrodes for both cortical and subcortical stimulation has been persistently difficult and often leads to no functional stimulation (1). This translational failure arises from the fact that the brain's immune environment and cellular makeup deviates starkly from those in peripheral tissues. In skeletal muscles, there is a good tolerance of foreign materials like biocompatible electrodes; however, in the brain-electrode interface, even the slightest inflammation leads to significant microglial activation, neuronal loss, and astrocytic scarring (**Figure 1**). The subsequent chronic foreign body response will prevent stable neuronal depolarization and proper ionic conductance due to the pro-inflammatory cytokines and reactive oxygen species (ROS) that are onset. Cumulatively, it is this loss of electrical coupling and encapsulation that is a leading cause of peripheral stimulating electrodes with intracranial applications (2,3).

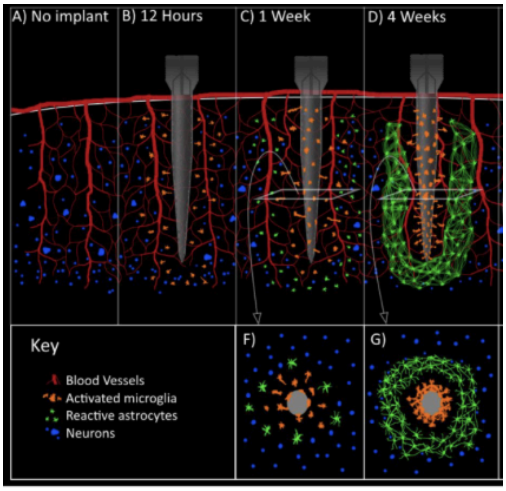

Figure 1: A visual representation of the immune response derived from an electrode

A2. The peripheral composition currently utilized fails from the fundamental differences in tissue structure and immune tolerance in intracranial regions leading to electrode drifting

Current FES peripheral electrodes are coated and insulated with nondegradable and stable polymers like polyurethane and silicones. The advantage of such a composition is that skeletal muscles tolerate these materials well leading to just a mild fibrosis and not evident functional loss present in the electrodes (4). These electrode exteriors certainly need to be nondegradable to stay structurally intact and supply their stream of current injections to the muscle tissues. But in the brain, where electrical functionality is more delicate and depends on just a millimeter or micrometer scale contact with neurons, the nondegradability aspect leads to complications. There will be induced shear stress, mechanical mismatch, and inflammatory activation that will lead to spatial drifting of the electrodes (5). It is the drifting that further amplifies a chronic inflammation from the silicone or polyurethane being nonintentionally grated off the electrode, exposing delicate and non-biocompatible electronic aspects of the peripheral electrode. This phenomenon not only rapidly deteriorates the performance of the electrode, but also completely jeopardizes the health of the patient (6,7). Such a translational gap evidently proves the need for external coatings that are able to dynamically tolerate the delicate neuroimmune environment of the brain that allows for secure electrode placement and protection.

A3. Biodegradable polymers can be engineered as external matrix coatings to minimize the inflammatory and oxidative damage at the electrode interface

As biomaterial research continues to advance, recent studies have demonstrated that biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) that can be used to release therapeutics to suppress immune responses and neutralize ROS (8). Specifically, these polymers can supply a

highly controlled drug and antioxidants delivery through the tuning of crosslinking density and degradation kinetics with specific consideration of phenol and thiol groups (9). Evidently, such biodegradable materials can serve as an external physical coating to preserve the mechanical integrity of the peripheral electrode, but also become a bioactive entity to maintain the ever-so important neural integrity of intracranial tissues. Though these design considerations have already been used to improve outcomes within implants in the periphery for FES patients, they are yet to be optimized as additional coatings within peripheral electrodes in the central nervous systems (9,10).

A4. BDNF and IL-10 act as highly potent therapeutics that address the specific neuroimmune demands of the brain's environment

Within the CNS, brain-derived neurotrophic factor (BDNF) and interleukin-10 (IL-10) serve as vigorous and potent molecules that can promote neuronal survival, while minimizing chronic inflammation. Particularly, BDNF will promote axonal regrowth, reinnervation, and integrity of the overall neural network, all while preventing the neuronal degeneration that arises from chronic glial scarring (**Figure 2**). IL-10, on the other hand, will directly inhibit TNF-α and IL-1, which are both pro-inflammatory cytokines, and also promote the creation of an M2 neuroprotective microglial phenotype to intensify tissue remodeling (11,12). Placing both BDNF and IL-10 therapeutics within a biodegradable ROS-scavenging polymer matrix like the engineered PLGA delivers both a neural regeneration mechanism and immune suppression that provides a *novel, but comprehensive* stability mechanism for the electrode-brain interface.

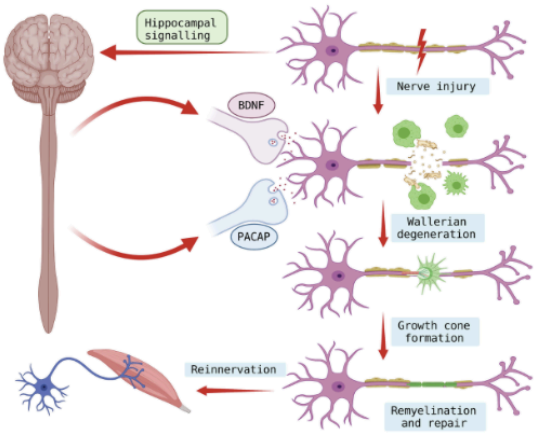

Figure 2: The mechanism on how BDNF can be utilized for reinnervation

A5. A broad economic and societal impact arises from the translation of existing electrodes into new patient populations .

Though there is an associated engineering novelty with such an approach, this particular research has very alluring economic and societal outcomes. By repurposing the already existing periphery electrodes, this approach can provide a scalable, low cost pathway for future FES within the brain, which accelerates the laboratory research into clinical application. Additionally, this approach reduces manufacturing costs since periphery electrode infrastructure is already mainstream, which reduces cost for both the research team and patients. This is especially important considering the continued population growth of traumatic brain injuries (TBI) and stroke individuals that can benefit from some motor control from FES, while having a lower burden of healthcare cost without sacrificing patient safety (13).

B. INNOVATION

B1. Dual-Function Coating: An integrated ROS scavenging matrix and therapeutic delivery coat for peripheral electrodes

Current research-grade electrode coatings are usually either just insulating the electrode surface or delivering a bioactive agent in a largely uncontrolled and unspecific manner (14). The innovation here lies in creating a biodegradable, dual-function polymer coating that will both scavenge ROS, and release neurotrophic/immunomodulatory factors in a tailored way. The coating will be primarily a PLGA-PCL matrix composite that can have tunable mechanical flexibility and degradation kinetics to match the intracranial environment for drift prevention. Specifically, the engineered ROS scavenging mechanism is from thiol and

catechol modifications that can neutralize the oxidative radicals near the electrode-brain interface (15). BDNF and IL-10 will then be encapsulated within the polymer matrix to provide neuronal support and immune suppression (16). Utilizing ROS buffering and therapeutic release would be the first dynamic approach to directly address the limitations in using peripheral electrodes in the brain.

B2. Establishing an electrode coating platform that can be scalable for a plethora of future research applications

A considerable benefit for this research is the tunability and modularity aspects that sets the foundation for subsequent customization of a diverse set of FES applications. The ROS-scavenging capacity, BDNF/IL-10 release, and biodegradation rate are all carefully engineered, such as altering the polymer molecular weight, coating thickness, and PLGA:PCL ratio. Such a broad range of tunability enables this technology to optimize in various neural locations and for different implantation durations, such as from short-term cortical arrays and chronic deep-brain stimulation, all while minimizing cost by using pre-existing electrodes as the base. Additionally, the potential fabrication that can be used like low-temperature crosslinking and dip coating are all completely compatible with the current electrode manufacturing modalities, which eliminates the need for new specialty equipment (17). The true innovation, therefore, lies in creating a straightforward and accelerated translation from preclinical research into subsequent clinical trials, creating a platform that reduces development cost and regulatory hurdles when compared to traditional electrode redesigns — the true innovation.

C. APPROACH

C1. Preliminary studies

C1A. Effectivity of PLGA and PCL as Bioactive Matrixes

Prior research has consistently demonstrated that PLGA-based matrixes were able to controllably release various therapeutic drugs in cancer studies. In this study, by altering the molecular weight and viscosity of PLGA, different yields of PDAc — a fluorescent indicator — and Paclitaxel — a chemotherapy drug — were released over a 30 day time span (**Figure 3)**. The experimental release of both PDAc and Paclitaxel matched predictive models exceedingly well due to the easily tunable nature of PLGA from the extensive studying that has been done on the material, highlighting its effectiveness a matrix coating; PCL is expected to generate nearly identicality predictable and effective results (18). Additionally, research has shown that both PLGA and PCL can be engineered from a biphasic to a zero-order release by altering molecular weight and end-group composition properties, which further provides precise control over degradation rates (19). Sustained degradation of just PLGA and PCL copolymer scaffolds has been estimated to last between 35 to 60 days; meanwhile, PLGA scaffolds releasing nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) have been able to provide on average of 38 days of controlled release (20, 21). This latter timeframe matches quite similarly with the post-implantation period when glial encapsulation is at its apex and neuroinflammation starts to become chronic between two and six weeks, which BDNF and IL-10 can help counteract (22).

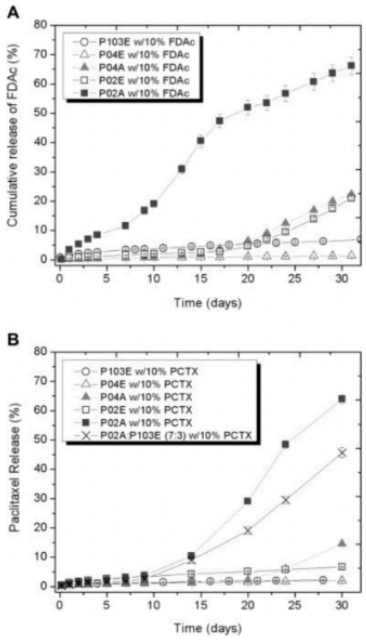

Figure 3: The variable release of FDAc (A) and Paclitaxel (B) with different PLGA variations

C2. Specific Aims

Specific Aim 1: Engineer and characterize biodegradable coatings that scavenge ROS and release IL-10/BDNF

Rationale and Hypothesis: Oxidative stress and chronic neuroinflammation will degrade the integrity and performance of peripheral-originated stimulators at the brain-electrode interface. Engineering a biodegradable PLGA:PCL matrix coating with ROS-scavenging motifs and being loaded with IL-10 and BDNF can provide a suitable electrode interface in intracranial regions. I hypothesize that peripheral electrode coatings that counteract ROS and deliver BDNF/IL-10 for 4-6 weeks will maintain neuronal health *in vito* when compared to single-function/uncoated peripheral-originated electrodes.

Experimental Design: To engineer the coatings, a 70:30 PLGA:PCL composite will be created with 2 to 5 wt% thiol and catechol groups for ROS scavenging and loaded with .5 to 1 µg of IL-10 and BDNF each (23). Using crosslinking at low temperatures and dip-coating techniques, the coatings will be applied to pre-existing platinum–iridium electrodes . Degradation and release kinetics will be evaluated over a 6 week span in 37°C PBS with the wt% of thiol/catechol and IL-10/BDNF µg varying as different experimental conditions. The control groups can simply be the single-function and uncoated peripheral-originated electrodes as benchmark comparisons. Cortical neuron–glia co-cultures will be placed on both the dual-function electrodes and the control electrodes; 100 ng/mL LPS + 10 ng/mL IFN-γ will then be used to induce inflammation (24). ROS scavenging can be found through DCFDA fluorescence, while βIII-tubulin and GFAP immunostaining can quantify neuronal health/glial activation, and PCR for Tnf can quantify cytokine expression (25).

Anticipated Results, Potential Problems, and Alternative Approaches: The dual-function coatings are expected to gradually degrade over 6 weeks, while maintaining a consistent BDNF/IL-10 release of 10–50 ng. Based on prior individual studies, ROS levels should decrease by 50% , pro-inflammatory cytokine expression should be reduced by 55 to 70%, and glial activation should decrease by 40% (25, 26). A potential problem can arise if the kinetics of a 70:30 PLGA:PCL composite degrade far faster than expected, and if this is the case a different composite ratio would need to be utilized. Additionally, if the ROS scavenging is insufficient, other scavenging groups or a higher concentration of the groups will need to be added.

Specific Aim 2: Evaluate the impact of coated electrodes on chronic brain neuroinflammation *in vivo*

Rationale and Hypothesis: The *in vitro* data from Aim 1 can show if polymer coatings will provide protection to neurons and the electrode, but there still requires translation into the full, complex environment of the brain that can only be done through an *in vivo* study. I hypothesize that the dual-function coated electrodes will reduce glial encapsulation, lower neuronal loss, and improve electrical performance compared to both single-function and uncoated peripheral-originated electrodes.

Experimental Design: Adults rats will have bilateral motor cortex implantation with one dual-function electrode on side and either a single-function or uncoated peripheral-originated electrode as the control on the other side. The rats will be sacrificed at the 2, 4, and 6 week time intervals post-implantation to harvest the brain tissues and analyze the acute/chronic immune responses. Microglial activation, neuronal survival, and oxidative stress can be quantified through a histological analysis. Additionally, glial-scar thickness will be measured around a 100 µm radius of the electrode-brain surface (27). Electrochemical impedance spectroscopy can further be used to analyze the electrode performance over the time intervals.

Anticipated Results, Potential Problems, and Alternative Approaches: The dual-function coated electrode are expected to significantly decrease neuroinflammation with both a 50% reduction in histological staining intensity and glial-scar thickness with the 100 µm radius, while also maintaining exceedingly more stable impedances compared to the controls within the rats (28). Like the prior aim, similar problems can arise with the PLGA:PCL ratios and insufficient ROS scavenging that can be alleviated in the same manner as before.

References:

[1] B. A. Karamian *et al.*, “The role of electrical stimulation for rehabilitation and regeneration after spinal cord injury,” *Journal of Orthopaedics and Traumatology*, vol. 23, no. 1, Jan. 2022, doi: https://doi.org/10.1186/s10195-021-00623-6

[2] G. C. McConnell, H. D. Rees, A. I. Levey, C.-A. Gutekunst, R. E. Gross, and R. V. Bellamkonda, “Implanted neural electrodes cause chronic, local inflammation that is correlated with local neurodegeneration,” *Journal of Neural Engineering*, vol. 6, no. 5, p. 056003, Oct. 2009, doi: https://doi.org/10.1088/1741-2560/6/5/056003.

[3] W. M. Grill and J. T. Mortimer, “Electrical properties of implant encapsulation tissue,” *Annals of Biomedical Engineering*, vol. 22, no. 1, pp. 23–33, Jan. 1994, doi: https://doi.org/10.1007/BF02368219.

[4] S. R. Bijwadia *et al.*, “Exploring skeletal muscle tolerance and whole-body metabolic effects of FDA-approved drugs in a volumetric muscle loss model,” *Physiological reports*, vol. 11, no. 12, Jun. 2023, doi: https://doi.org/10.14814/phy2.15756

[5] B. T. Seaton, D. F. Hill, S. L. Cowen, and M. L. Heien, “Mitigating the Effects of Electrode Biofouling-Induced Impedance for Improved Long-Term Electrochemical Measurements In Vivo,” *Analytical Chemistry*, vol. 92, no. 9, pp. 6334–6340, Apr. 2020, doi: https://doi.org/10.1021/acs.analchem.9b05194

[6] S. Szunerits, Q. Pagneux, Youssef Ben M'Barek, S. Vassal, and Rabah Boukherroub, “Do not let electrode fouling be the enemy of bioanalysis,” *Bioelectrochemistry*, vol. 153, pp. 108479–108479, May 2023, doi: https://doi.org/10.1016/j.bioelechem.2023.108479

[7] J. Männlin *et al.*, “Safety profile of subdural and depth electrode implantations in invasive EEG exploration of drug-resistant focal epilepsy,” *Seizure*, vol. 110, pp. 21–27, Jun. 2023, doi: https://doi.org/10.1016/j.seizure.2023.05.022

[8] A. Platel, R. Carpentier, E. Becart, G. Mordacq, D. Betbeder, and F. Nesslany, “Influence of the surface charge of PLGA nanoparticles on their in vitro/genotoxicity, cytotoxicity, ROS production and endocytosis,” *Journal of Applied Toxicology*, vol. 36, no. 3, pp. 434–444, Oct. 2015, doi: https://doi.org/10.1002/jat.3247

[9] T. Chen *et al.*, “Biodegradable stimulating electrodes for resident neural stem cell activation in vivo,” *Biomaterials*, vol. 315, p. 122957, Nov. 2024, doi: https://doi.org/10.1016/j.biomaterials.2024.122957.

[10] H. Yu *et al.*, “Development of a rapidly made, easily personalized drug-eluting polymer film on the electrode array of a cochlear implant during surgery,” *Biochemical and Biophysical Research Communications*, vol. 526, no. 2, pp. 328–333, May 2020, doi: https://doi.org/10.1016/j.bbrc.2020.02.171.

[11] C. Qin, Z. Yue, R. J. Forster, J. Chen, and G. G. Wallace, “On demand, wireless electrochemical release of brain derived neurotrophic factor,” *Electrochemistry Communications*, vol. 157, p. 107626, Nov. 2023, doi: https://doi.org/10.1016/j.elecom.2023.107626.

[12] S. S. Iyer and G. Cheng, “Role of Interleukin 10 Transcriptional Regulation in Inflammation and Autoimmune Disease,” *Critical Reviews™ in Immunology*, vol. 32, no. 1, pp. 23–63, 2012, doi: https://doi.org/10.1615/critrevimmunol.v32.i1.30.

[13] J. Yan, C. Wang, and B. Sun, “Global, regional, and national burdens of traumatic brain injury from 1990 to 2021,” *Frontiers in Public Health*, vol. 13, Apr. 2025, doi: https://doi.org/10.3389/fpubh.2025.1556147

[14] P. Yin, Y. Liu, L. Xiao, and C. Zhang, “Advanced Metallic and Polymeric Coatings for Neural Interfacing: Structures, Properties and Tissue Responses,” *Polymers*, vol. 13, no. 16, p. 2834, Aug. 2021, doi: https://doi.org/10.3390/polym13162834. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8401399/

[15] H. Shin, H. Satsu, M.-J. Bae, M. Totsuka, and M. Shimizu, “Catechol Groups Enable Reactive Oxygen Species Scavenging-Mediated Suppression of PKD-NFkappaB-IL-8 Signaling Pathway by Chlorogenic and Caffeic Acids in Human Intestinal Cells,” *Nutrients*, vol. 9, no. 2, p. 165, Feb. 2017, doi: https://doi.org/10.3390/nu9020165.

[16] Z. González, A. Ferrandez-Montero, and J. Domínguez-Robles, “Recent Advances in Polymers as Matrices for Drug Delivery Applications,” *Pharmaceuticals*, vol. 16, no. 12, p. 1674, Dec. 2023, doi: https://doi.org/10.3390/ph16121674.

[17] Fatma Ben Dhieb, S. H. Tabatabaei, Frej Mighri, and Abdellah Ajji, “Comparison of Crosslinking Efficiency in Dip and Roll-Deposited Coatings on Their Oxygen Barrier,” *ACS Omega*, vol. 4, no. 14, pp. 15772–15779, Sep. 2019, doi: https://doi.org/10.1021/acsomega.9b00950

[18] C. L. Huang *et al.*, “Modulating drug release from poly(lactic-co-glycolic acid) thin films through terminal end-groups and molecular weight,” *Polymer Degradation and Stability*, vol. 98, no. 2, pp. 619–626, Nov. 2012, doi: https://doi.org/10.1016/j.polymdegradstab.2012.11.012.

[19] Z. Yang *et al.*, “Design of a zero-order sustained release PLGA microspheres for palonosetron hydrochloride with high encapsulation efficiency,” *International Journal of Pharmaceutics*, vol. 575, p. 119006, Feb. 2020, doi: https://doi.org/10.1016/j.ijpharm.2019.119006

[20] R. de Boer, A. M. Knight, R. J. Spinner, Martijn J. A. Malessy, M. J. Yaszemski, and A. J. Windebank, “*In vitro* and *in vivo* release of nerve growth factor from biodegradable poly-lactic-*co*-glycolic-acid microspheres,” *Journal of Biomedical Materials Research Part A*, vol. 95A, no. 4, pp. 1067–1073, Sep. 2010, doi: https://doi.org/10.1002/jbm.a.32900.

[21] A. Aubert-Pouëssel *et al.*, “In vitro study of GDNF release from biodegradable PLGA microspheres,” *Journal of Controlled Release*, vol. 95, no. 3, pp. 463–475, Mar. 2004, doi: https://doi.org/10.1016/j.jconrel.2003.12.012

[22] J. W. Salatino, K. A. Ludwig, T. D. Y. Kozai, and E. K. Purcell, “Glial responses to implanted electrodes in the brain,” *Nature Biomedical Engineering*, vol. 1, no. 11, pp. 862–877, Nov. 2017, doi: https://doi.org/10.1038/s41551-017-0154-1

[23] Z. G. Tang, N. P. Rhodes, and J. A. Hunt, “Control of the Domain Microstructures of PLGA and PCL Binary Systems: Importance of Morphology in Controlled Drug Release,” *Chemical Engineering Research and Design*, vol. 85, no. 7, pp. 1044–1050, Jan. 2007, doi: https://doi.org/10.1205/cherd06217

[24] A. E. Maluish *et al.*, “The determination of an immunologically active dose of interferon-gamma in patients with melanoma.,” *Journal of Clinical Oncology*, vol. 6, no. 3, pp. 434–445, Mar. 1988, doi: https://doi.org/10.1200/jco.1988.6.3.434

[25] G. Sgarbi, G. Gorini, A. Costanzini, S. Barbato, G. Solaini, and A. Baracca, “Hypoxia decreases ROS level in human fibroblasts,” *The International Journal of Biochemistry & Cell Biology*, vol. 88, pp. 133–144, Jul. 2017, doi: https://doi.org/10.1016/j.biocel.2017.05.005.

[26] C. T. Tsui, P. Lal, K. V. R. Fox, M. A. Churchward, and K. G. Todd, “The effects of electrical stimulation on glial cell behaviour,” *BMC Biomedical Engineering*, vol. 4, no. 1, Sep. 2022, doi: https://doi.org/10.1186/s42490-022-00064-0

[27] E. Moeendarbary *et al.*, “The soft mechanical signature of glial scars in the central nervous system,” *Nature Communications*, vol. 8, p. 14787, Mar. 2017, doi: https://doi.org/10.1038/ncomms14787

[28] C.-T. Tan *et al.*, “Real-time measurement of electrode impedance during intracochlear electrode insertion,” *The Laryngoscope*, vol. 123, no. 4, pp. 1028–1032, Mar. 2013, doi: https://doi.org/10.1002/lary.23714