Biofunctionalized carbon nanotubes as a smart nanomaterial immobilized on ~~a~~ tissue ~~-~~culture polystyrene plate**s** for promoting neuronal outgrowth

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Abstract

Carbon nanotubes (CNTs) ~~offer~~ exhibit attractive attributes that ~~are~~ make them useful ~~in~~ as an innovative biomate~~e~~sign for neuroscience research. ~~-~~These include their ~~due to their~~ nanoscale features, modifiable chemical functionality~~ties~~, and tunable electrical properties. In this study, we developed a simple and cost-effective ~~fabrication~~ method for ~~advanced~~ fabricating surface-modified cell culture system**s** by immobilizing biofunctionalized CNTs onto commercial tissue ~~-~~culture polystyrene plates. ~~-~~This active substrate was then examined to understand ~~the effects o~~how~~f~~ electrical, morphological, and chemical interactions with a CNT-entrapp[illegible] phosphatase and tensin homolog deleted on chromosome 10 (~~drug, bpV,~~ ~~as a~~ PTEN) inhibitor, namely, bisperoxovanadium (bpV), affect ~~on~~ the neuronal differentiation of PC-12 cells. Compared ~~to~~ with the control, the percentage of neuronal cells ~~stimulating~~ bearing neurites increased by a ~~a~~ factor of 4.0, 7.8, and 10.0~~,~~ ~~respectively,~~ when cultured~~-~~, respectively, on an immobilized carboxylated CNT substrate, a poly(ethylene glycol) (PEG)ylated CNT substrate~~PEGylated CNT substrate~~, and a bpV-loaded PEGylated CNT substrate, ~~respectively, in the presence of~~ (10 nM bpV)~~, respectively~~. The bpV-loaded CNT substrate**s** do[illegible]gulated the expression of PTEN and ~~up-regulated~~activated the Akt/ERK signaling pathway~~,~~ thereby providing ~~the~~ a mechanism for the improved neuronal outgrowth. ~~-~~These results highlight the promise of ~~the~~ biofunctionalized CNTs as ~~the~~ an electroactive and drug-releasing smart nanomaterial**s** for promoting neuronal outgrowth and suggest ~~their~~ that they ~~have potential for~~ may be ~~use in~~useful in ~~potential utility in~~ future neural regeneration applications.

Keywords: carbon nanotube**s**, biofunctionalization, surface~~-~~-modified tissue culture plate, drug delivery system, PTEN inhibitor, neuronal outgrowth, neural regeneration

Please consider mentioning some of these features explicitly.
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Define abbreviations at first use in both the abstract and the main text. Please also note the correct expansion of PTEN.
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Please note that you activate or enhance signaling through a pathway; the pathway itself is not up-regulated.
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1. Introduction

Parallel advances in nanotechnology and tissue engineering over the past decades have ~~demanded~~ spurred the ~~innovative~~ design**s** ~~of~~ and development of smart biomaterials through multidisciplinary approaches ~~and promoted development~~. Numerous convergence ~~studies~~ studies have been attempted to regenerate neural tissue, one of the most difficult ~~areas~~ tasks in tissue engineering and regenerative medicine.

Bioinspired nanocomposites for nerve tissue repair ~~or~~ and neural regeneration require substrates ~~with~~ that exhibit several key properties. These include~~appropriate~~ topographical surfaces, improved attachment to neuronal cells for proliferation and/or differentiation, and the capacity for the sustained release of biofunctional factors. These~~,~~ ~~and~~ ~~as well as certain indispensable features,~~materials should also exhibit ~~including~~ mechanical integrity, controllable biodegradability, and good biocompatibility with the nanoscale reinforcements that are being

applied for aemployed in a broad range of applications [1–8].

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Among the various nanomaterials being explored, carbon nanotubes (CNTs), which possess unique electrical, mechanical, physical, and chemical prope has are a been a popular component choice for smart biomaterials design. CNTs are already being used in A variety of applications in various basic and applied neuroscience research rely on CNTsapplications [9–14]; however, concerns remain relating to theregarding the cytotoxicity and genotoxicity of CNTs in the context ofwith respect to both in vitro*in vitro* and in vivo*in vivo* applications still remain [15–19]. CNT The toxicity of CNTs may be ntered resolved by modifying them CNT nanomaterials with biocompatible moieties and by immobilizing the CNTs onto the surfaces of other materials for suitable for biomedical applications [20].

Thus, the Biofunctionalization biofunctionalization of CNTs may can address their toxicity issue, while alsoand at the same time it can also expanding their functionality of CNTs by promoting cell attachment, neuronal outgrowth, neuronal differentiation, and nerve tissue regeneration [21]. Interactions between neural cells and CNT substrates, which are used as an alternative to theto directly addingtion of CNTs to the neuronal culture medium, have been explored in an effort to reduce the toxicity of CNTs and improve the utility oftheir utility CNTs in implantable devices or and cell-guiding scaffolds [14, 22].

Significant efforts have been applied made to toward develop drug delivery systems, in which that allow drugs are to be delivered to the target tissue or cells. Efficient drug capture systems based on CNT substrates require polyethylene glycol (PEG) coatings, that is, PEGylation, to enable allow for the incorporation of both water-insoluble or and water-soluble drugs for controlled release into an aqueous medium via nanoscale extraction and toto improve neural regeneration [23–25]. The PEGylation of CNTs, which are hydrophobic, improves their solubility of the hydrophobic nanotubes by increasing the dispersibility as well asand increases their hydrodynamic size, and decreases their immunogenicity, thereby reducing their cytotoxicity [18, 26]. This work describes an efficient system for loading and releasing the drug, bisperoxovanadium (bpV), which acts as a potent inhibitor of the protein tyrosine phosphatase (PTPase) activity of potent PTPase inhibitor of phosphatase and phosphatase and tensin homolog deleted from on chromosome 10 (PTEN) as well as an enhancer of neurite outgrowth [27–29].

Please note that CNTs don't dissolve, they disperse. "Solubility" implies a molecular-level solution; what you have is a colloidal suspension of tubes held apart by surfactant or functionalization.
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Please note that the standard expansion of PTEN uses "on," not "from."
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This study explores the use of biofunctionalized CNT substrates in enhancing neuronal cell outgrowth. Five Four stages types of CNT substrates were addressedevaluated: i) a the commercial culture plate (CP) and pristine CNTs, ii) a CP with functionalized CNTs with subjected to carboxylation and covalent crosslinking onto the CP surface of CP (CP-CNT-COOH), iii) PEGylation of CNTs subjected to PEGylation (CP-CNT-PEG-NH_2), and iv) biofunctionalized CNTs biofunctionalized by loading and releasing the drugs on the a PEGylated CNT substrate (CP-CNT-PEG + drug) for a smart drug delivery system (DDS). and v) Vvarious analyses of the neuralneuronal outgrowth analysis were then performed to assess the potential of these biofunctionalized CNT substrates affected by CNTs for nerve tissue regeneration and biomedical applications (Fig. 1). For each substrate, We we assessed screened cell viability and, various analysis ofanalyzed neuronal outgrowth, drug-stimulated differentiation, and the underlying pathways activated in the cells culturedcultured cells. on each biofunctionalized CNT substrate. The nNeuronal outgrowth from the neuronal cells was promoted by the electrical conductivity of the CNT substrates under theand the controlled effective release of the drugs.

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