Conducting Polymer Microcavities for Controlled Release of Antineoplastic Agents to Brain Tumors

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Statement of Purpose: Despite significant progress in development of new chemotherapeutic agents and methods of dug delivery, the effective therapy for treatment of brain tumors remains a challenge [1]. To overcome the blood brain barrier problem, high doses of systemic intravenous delivery of anticancer drugs are required, that can cause adverse side effects. It is becoming clear that a major unmet challenge for the field is to develop methods that allow effective and local delivery of chemotherapeutic agents in cellular level [2]. In this study we report a novel method for local and on-demand release of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) using electrical actuation of conducting polymer on the surface of microelectrodes. Conducting polymers have been widely used in biomedical applications, in particular, for drug delivery systems and neural interfaces [3, 4]. This innovative technology allows for a more precise release of anticancer agent at the tumor sites.

Methods: Our novel drug delivery system was constructed by forming a thin layer of poly (3,4-ethylenedioxythiophene) (PEDOT) around the BCNU-loaded poly(lactic-co-glycolic) PLGA microspheres (**Fig. 1a**). PLGA microspheres loaded with BCNU were prepared through electrospraying technique [4]. A mixture of 617 mg PLGA and 31 mg BCNU was added to 10 mL chloroform to prepare a homogenous solution with a concentration of 4% (w/w) PLGA. PLGA-BCNU microspheres were directly deposited on gold sites of neural microelectrodes. After scaffold fabrication, EDOT was electropolymerized on each electrode site and around the PLGA-BCNU microspheres. The electrochemical deposition of PEDOT was carried out with an applied current density of 0.5 mA/cm^2 for 12 min by using a conventional four-electrode configuration at room temperature. After creating the desired morphology, Field Emission Scanning Electron Microscopy (FESEM) images were taken to visualize the surface morphology of the PEDOT microcavities (Fig 1b,c). In order to show improvement of electrical property of gold sites, impedance of electrode sites were recorded using an electrochemical impedance spectroscopy. Finally, BCNU-loaded PEDOT microcavities were actuated to release the BCNU by applying a positive voltage of 1 V. Release profile of BCNU from PLGA microspheres and PEDOT microcavities was monitored in a phosphate buffered solution at 37°C using UV-vis Spectrophotometer.

Results: We successfully demonstrated that we were able to control the size of PLGA microspheres and thickness of PEDOT microcavities by adjusting electrospraying and electrochemical deposition parameters, respectively. FESEM images revealed that the size of PLGA-BCNU microspheres and the wall thickness of PEDOT microcavities ranged from 1 to 3 μm and 50 nm to 100 nm, respectively (Fig. 1b,c). Impedance spectroscopy

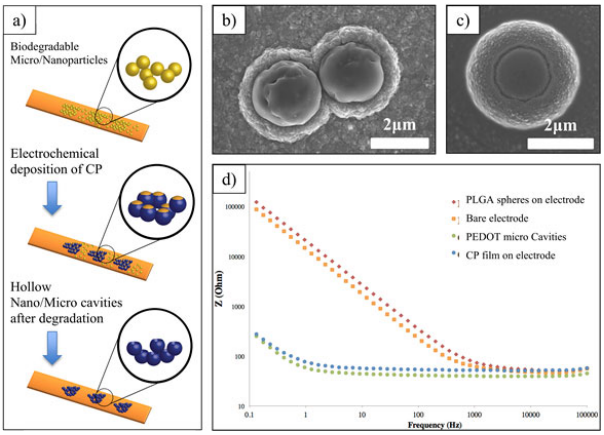

Figure 1. a) Schematic image of fabrication of PEDOT microcavity platforms, b,c) SEM image of PLGA microspheres wrapped with PEDOT shell, d) Impedance spectroscopy of gold and modified sites.

results indicated impedance of PEDOT microcavities-coated gold sites significantly decreased with an increasing in frequency over the range of 1-10^5 Hz. Also we showed that the impedance of electrodes increased after electrospraying of PLGA (Fig. 1d). UV spectrophotometry experiment revealed about 75% of the BCNU was released from PLGA microspheres after 85 hr, as a result of diffusion of the drug through the degraded PLGA microspheres. We found that adding the PEDOT sheath layer dramatically slowed down the drug release profile. Furthermore, we demonstrated that BCNU was precisely triggered by electrical actuation of PEDOT microcavities with an applied voltage of 1V.

Conclusions: Our preliminary results indicated a significant release of BCNU from PLGA microspheres due to the fast hydrolytic degradation of PLGA. Adding a PEDOT layer as a shell around the BCNU-loaded PLGA spheres dramatically decreased the rate of BCNU release. Finally, on-demand and precisely triggered release of BCNU was observed during electrical stimulation of the PEDOT microcavities. This innovative drug delivery system holds a considerable promise for precisely and on-demand release of anticancer agents at the tumor sites to minimize the drug side effects. Future study will focus on effect of on-demand release of BCNU on brain tumor cells both *in vitro* and *in vivo*.

References:

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