



## Semi-interpenetrating network of polyethylene glycol and photocrosslinkable chitosan as an in-situ-forming nerve adhesive

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### ABSTRACT

An ideal adhesive for anastomosis of severed peripheral nerves should tolerate strains imposed on rejoined nerves. We use blends of photocrosslinkable 4-azidobenzoic acid-modified chitosan (Az-C) and polyethylene glycol (PEG) as a new in-situ-forming bioadhesive for anastomosing and stabilizing the injured nerves. Cryo-scanning electron microscopy suggests that the polymer blends form a semi-interpenetrating network (semi-IPN), where PEG interpenetrates the Az-C network and reinforces it. Az-C/PEG semi-IPN gels have higher storage moduli than Az-C gel alone and fibrin glue. Nerves anastomosed with an Az-C/PEG gel tolerate a higher force than those with fibrin glue prior to failure. A series of ex vivo and in vitro cell experiments indicate the Az-C/PEG gels are compatible with nerve tissues and cells. In addition, Az-C/PEG gels release PEG over a prolonged period, providing sustained delivery of PEG, a potential aid for nerve cell preservation through membrane fusion. Az-C/PEG semi-IPN gels are promising bioadhesives for repairing severed peripheral nerves not only because of their improved mechanical properties but also because of their therapeutic potential and tissue compatibility.

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### 1. Introduction

Traumatic peripheral nerve injuries occur by blunt trauma and foreign object penetration, often resulting in complete or partial transection of the nerve [1,2]. These nerve injuries inflict significant economic and social burdens. The injured nerves are typically treated by surgical techniques, but the clinical outcome is not always satisfactory. Reportedly ~50% of the patients with nerve injuries showed good to excellent results or useful recovery after treatments, but 25–30% reported poor outcomes [3–6]. Therefore, an effective therapy of peripheral nerve injuries is eagerly awaited.

A standard procedure is to coapt the severed nerves by microsurgical suture [7]. A weakness of this technique, however, is that the suturing procedure involves multiple needle passages through the epineurium and results in structural disturbance in the nerves. Additionally, non-absorbable suture materials may cause foreign body reactions and scar tissue formation [8,9], which can interfere with the axonal regeneration and the nerve function after healing

[8,10]. Fibrin glue has been proposed as a potential replacement for sutures and has been welcomed as a simple and effective anastomosis technique [11–18]. However, the risk of disease transmission [19] and its weak mechanical strength [20] remain serious impediments to its use. Intense laboratory and clinical investigations have continuously improved the outcomes of nerve repair, but more effective methods to repair nerve injuries are still in high demand.

In an attempt to overcome some of the disadvantages of fibrin glue, we previously proposed a hydrogel based on photocrosslinkable chitosan (Az-C), prepared by partial conjugation of 4-azidobenzoic acid (ABA) to chitosan [21], as an alternative nerve adhesive [22,23]. Aqueous solution of Az-C forms a hydrogel upon ultraviolet (UV) illumination, which induces photolytic conversion of aryl azide to reactive nitrene, which undergoes ring expansion and reacts with the amines of Az-C to form an inter- and intramolecular chitosan network [22]. Chitosan hydrogel is an attractive substitute for fibrin glue or suture, due to its simplicity of application, tissue adhesiveness [24], safety and biocompatibility [25,26]. Our prior study showed that the Az-C gels were compatible with cultured neural cells and could reconnect nerves with mechanical properties comparable to fibrin glue [22]. However, further improvement in the mechanical strength would be desirable for the Az-C gels to provide reliable support for the anastomosed nerves during the critical healing period.

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