Simple and Effective Non-Thrombogenic Surface Modifications using Macro Zwitterionic Surface Modifiers for Metallic Blood Contacting Devices

Sang-Ho Ye, Carl A. Johnson Jr, Joshua R. Woolley, Venkat Shankarraman and William R. Wagner
McGowan Institute for Regenerative Medicine, Depts. of Bioengineering & Surgery
University of Pittsburgh, Pittsburgh, PA 15219 USA.

Statement of purpose: Enhancing surface blood compatibility on clinically utilized metallic surfaces, such as titanium alloys, could reduce thrombotic complications associated with existing devices and facilitate the application of metallic materials in new settings. Previously, we reported that covalently modified titanium alloy ($TiAl_6V_4$) surfaces with zwitterionic phosphorylcholine (PC) or sulfobetaine (SB) moieties could significantly reduce surface thrombotic deposition [1, 2]. A simple modification process using a bifunctional modifier might be advantageous in the manufacturing process for cardiovascular devices with complicated geometries or for biodegradable metallic surfaces that require rapid, mild processing. Our objective here was to synthesize novel macro surface modifiers that have macro PC or SB moieties and siloxane groups in their structure by a thiol-ene radical transfer polymerization technique [3]. The effectiveness of the created macro PC or SB modifiers was evaluated in terms of the effect of modification on platelet deposition and activation in vitro.

Methods: Macro-PC or SB modifiers with siloxane functional groups (PCSSi and SBSSi) were synthesized by UV irradiation after adding benzophenone as a photocatalyst, 3-mercaptopropyl) trimethoxysilane (MPTMSi) and 2-methacryloyloxyethyl-phosphorylcholine (MPC) or *N*-(3-sulfopropyl)-*N*-(methacryloxyethyl)-*N, N*-dimethylammonium betaine (SMDAB) monomers with a defined monomer ratio (PCSSi(5) or SBSSi (5): MPTMSi and MPC(or SMDAB) monomer ratio = 1:5). PCSSi and SBSSi chemical structures were confirmed with ^{1}H NMR. A passivated titanium alloy ($TiAl_6V_4$) surface was directly modified by PCSSi or SBSSi via an anhydrous liquid phase deposition method. The modified surfaces were characterized by X-ray photoelectron microscopy (XPS). Surface thrombotic deposition and platelet activation on the surfaces was assessed after in vitro ovine blood contact by scanning electron microscopy (SEM) and deposited platelet quantification by lactate dehydrogenase (LDH) assay.

Results: XPS surface analysis of modified Ti-PCSSi (5) showed increased nitrogen (N=2.5±0.6) and phosphorus (P=2.3 ± 0.8) relative to $TiAl_6V_4$ (N=1.0±0.5; P=0.1±0.2) ($p<0.05$). The data also support the successful modification of $TiAl_6V_4$ surfaces with the SB groups based on an increased nitrogen (N=2.2±0.4) and sulfur composition (S=2.8 ± 1.0) on the surface of Ti-SBSSi (5). **Fig. 1** provides representative micrographs of the observed platelet deposition after ovine blood contact. Platelet deposition quantified by the LDH assay is shown in **Fig. 2**. The unmodified $TiAl_6V_4$ surface showed relatively high deposition of activated platelets. However, the deposition on Ti-PCSSi (5) and Ti-SBSSi (5) surfaces was markedly decreased compared to the unmodified Ti ($p<0.01$). Deposited platelet numbers on the Ti-PCSSi (5) and Ti-SBSSi (5) surfaces were equal to or lower than that for PC or SB modified surfaces where more complex surface polymerization or modifier synthesis were required [1, 2].

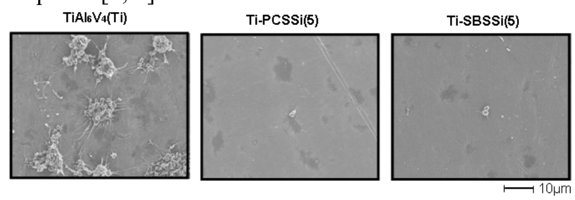

Fig. 1 SEM micrographs of modified and unmodified $TiAl_6V_4$ samples after fresh ovine blood contact for 2 h at 37ºC.

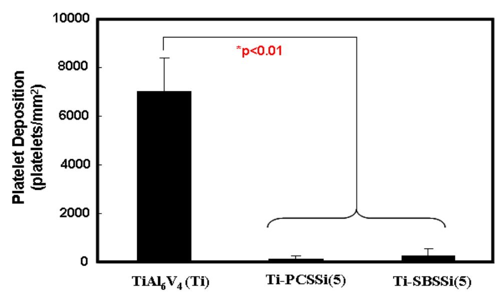

Fig. 2 Platelet deposition on unmodified and modified $TiAl_6V_4$ samples after 2 h blood contact quantified by LDH assay.

Conclusions: Bifunctional macro-PC or SB modifiers (macro-PCSSi (or SBSSi) were successfully prepared by a thiol-ene radical transfer polymerization technique. Surface modification using the macro-PCSSi or SBSSi modifiers was attractive due the simplicity of the processing and the effectiveness of the modification in reducing thrombogenicity. In comparison to other surface modification techniques which require multiple or complicated processing the described method offers relative ease of development and application for complex surface shapes associated with some metallic devices and should be applicable for biodegradable metallic surfaces.

Acknowledgements & References: Funding: NIH contract #HHSN268200448192C and NSF Engineering Research Center for Revolutionizing Metallic Biomaterials (Award #0812348).

1. Ye SH et al. *Colloids Surf. B: Biointerfaces* 2009, 74:96.
2. Ye SH et al. *Colloids Surf. B: Biointerfaces* 2010, 79:357.
3. Lecamp L et al. *Polymer* 2001,42:2727.