In Vitro and *In Vivo* Assessment of Fluorinated Polyphosphazene Catheter Coatings

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Statement of Purpose: Biomaterial associated thrombosis is the most common complication for blood contacting medical devices. Polyphosphazenes (PPs) are high polymers comprised of an alternating phosphorous-nitrogen backbone and can have different properties by changing side groups on the P-N backbones. Our prior work has developed crosslinkable poly[bis(octafluoropentoxy) phosphazene (X-OFP) which can improve the mechanical properties compared to traditional fluorinated poly[bis(trifluoroethoxy) phosphazene] (TFE) and significantly reduce the formation of biofilm and inhibit thrombosis.[1] This study was to assess this fluorinated polyphosphazene in vitro and in vivo for use as coatings on commercial implantable devices such as catheters to reduce the formation of thrombosis.

Methods: Non-crosslinkable TFE and crosslinkable X-OFP polymers were synthesized for this study. Commercial polyurethane catheters (AK-04210, ARROW) were coated with polyphosphazenes by dipping twice. Water contact angle, AFM, and XPS were used to assess the properties of the polyphosphazene-coated catheter surfaces. An *in vitro* blood flow loop system using whole bovine blood driven by an 8-channel pump was used to measure the blood thrombosis response to catheters.[2] A total of ~120 mL bovine whole blood in each channel was circulated at 37°C for 20h at flow rate of 100 mL/min. The clotting areas on catheters were imaged and analyzed by Image J. A New Zealand white rabbit model was used to assess the biocompatibility of catheter which was introduced into the jugular vein for 7 days. Pictures of the exterior, blood-contacting surface of the catheters were examined by the Image J program to measure the thrombus area on catheter surfaces.

Results:

Characterization of polyphosphazene coating.
AFM phase images show the phase separation of the fluorinated polyphosphazene. The Young's modulus measured by AFM show that the crosslinking significantly improved mechanical properties of X-OFP coating. XPS analysis shows the polymers contained the chemical species expected based on the chemical structures. Both TFE and X-OFP coatings are hydrophobic with water contact angles in the range of 96-106° due to the fluorocarbon characteristics.

In vitro blood responses to polyphosphazene coating: plasma coagulation and thrombosis.
Coagulation time of human plasma in contact with catheters show that PU control had a shorter time than the blank (without catheter) while the polyphosphazene coated catheters exhibited longer coagulation times than the blank, indicating the fluorinated PP coatings reduced plasma coagulation. The increase of coagulation time is believed to be due to plasma protein adsorption to the hydrophobic fluorinated catheters resulting in loss of plasma coagulation (Fig. 1A). The clotting areas on the catheter surfaces in blood flow loop experiments were all normalized to Control PU catheters (Fig. 1B). Results show that the fluorinated polyphosphazene coatings significantly reduced the thrombosis formation on surfaces.

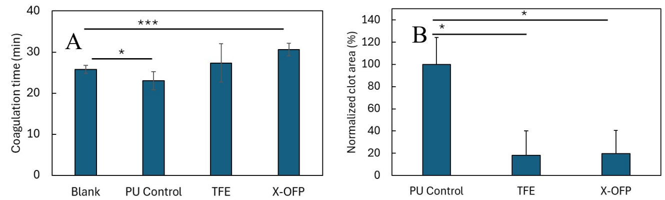

Fig. 1. (A) Coagulation time of plasma in contact with catheters. (B) The clotting area of thrombosis formed on catheter surfaces in in vitro blood loop system for 20h (area normalized to PU control).

In vivo assessment of thrombus formation on catheters in the rabbit model. The catheters were implanted in rabbit jugular vein for 7 days. Images of the interior morphology of the vein with the catheter (Fig. 2A) were taken after explantation. The thrombus formation was highlighted, and its surface area was calculated using Image J (Fig. 2B). Results show that polyphosphazenes-based material demonstrated significant improvement in preventing clot formation within the jugular vein. There's no difference observed between TFE and X-OFP groups, suggesting that X-OFP improved the mechanical properties of fluorinated polyphosphazene coatings, but retained the same good hemocompatibility as TFE.

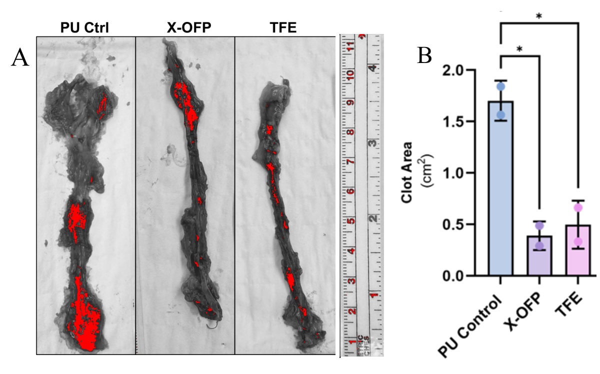

Fig. 2. (A) Representative images of PU control, X-OFP and TFE coated catheters after explantation. The jugular vein was cut longitudinally to show thrombus formation on the interior of the vessel (highlighted region). (B) Quantitative analysis of total clot area formed on the internal jugular vein for control and PP coated catheters.

Conclusion:

Fluorinated polyphosphazenes slow plasma coagulation and decrease thrombosis on catheters. X-OFP can create a complete, strong coating over commercial medical devices, providing a long-term protective coating for medical blood contact implant devices.

References:

[1] Alwine et al. *J Biomed Mater Res*. 2023;111:1533–1545.
[2] Wu et al. *Acta Biomater*. 2024; 180:372-382.

Acknowledgements:

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