

Oral presentation

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Thrombin inhibitor perfluorocarbon nanoparticles for treatment and ^{19}F tracking of acute thrombosis

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Introduction

Localized thrombus formation as a consequence of cardiovascular disorders can lead to acute arterial or venous occlusions. Heparin is the standard medication in emergency treatment of occlusive events, but optimization of antithrombotic mediation of acute thrombi remains a significant research challenge.

Methods

Perfluorocarbon (PFC) nanoparticles (NPs) were functionalized via covalent attachment of the irreversible thrombin inhibitor, PPACK (Phe(D)-Pro-Arg-Chloromethylketone). Particle-PPACK coupling was verified through zeta potential measurement and HPLC quantification. Inhibition of thrombin cleavage of Tosyl-Gly-Pro-Arg-4 nitrilide acetate was assessed via optical assay to verify that PPACK activity against thrombin and selectivity for thrombin over plasmin was not diminished on attachment to the particles. PPACK NPs ($n = 7$), PPACK ($n = 4$), heparin ($n = 4$), non-functionalized NPs ($n = 7$), and saline ($n = 7$) were used to treat C57BL6 mice immediately following laser injury of the carotid artery. Time to thrombotic occlusion of the injured artery was assessed via Doppler flow measurement. For selected mice receiving NPs, particle retention in extracted carotid arteries was assessed via ^{19}F MRS/MRI at 11.7 T.

Results

PPACK activity against and specificity for thrombin was verified before and after coupling to PFC NPs. In our mouse injury model, PPACK and non-functionalized NPs failed to significantly delay time to occlusion of the

carotid artery. Heparin delayed occlusion to a degree predicted by previously published data. PPACK NPs significantly outperformed both heparin ($p = .001$) and PPACK ($p = .0006$) in delaying occlusion of the carotid artery (Figure 1). Quantitative ^{19}F MRS indicated the presence of more PFC NPs in occluded arteries of animals treated with PPACK NPs (Figure 2) than in injured arteries of mice treated with non-functionalized NPs. Uninjured arteries from the same animals produced no ^{19}F signal.

Conclusion

In our model, PPACK-functionalized PFC NPs surpassed heparin in treatment of acute thrombosis. The particles take advantage of PPACK's high affinity and specificity for thrombin while utilizing the vascular confinement and long circulating half-life of the PFC NPs. ^{19}F MRS and MRI

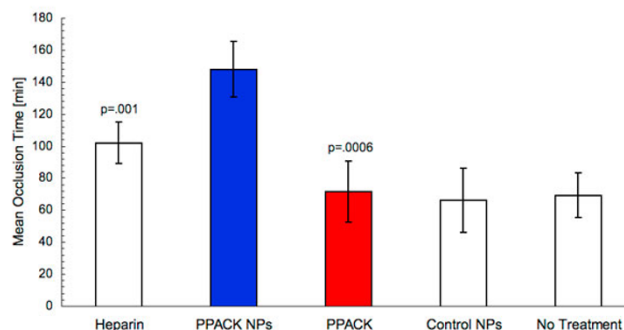


Figure 1

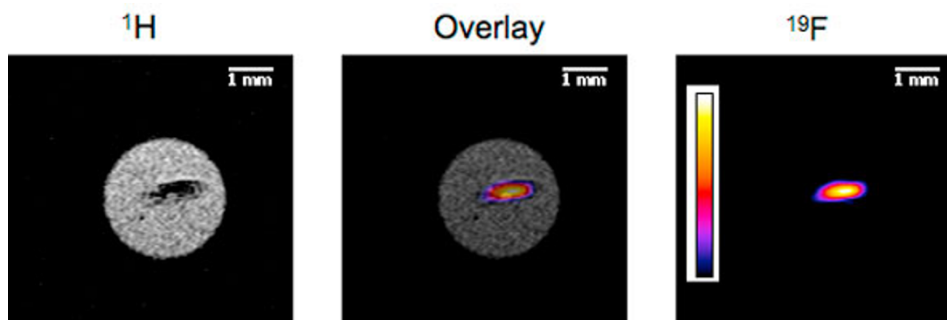


Figure 2

indicate that PPACK NPs are retained in forming clots. As a potent antithrombotic that can be traced with ^{19}F MRS and MRI, PPACK NPs have great therapeutic potential.

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