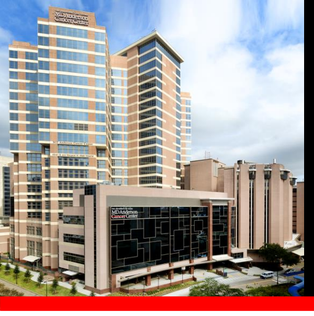

Radiopaque Nanoparticle and Dipyridamole-loaded Electrospun Polymeric Scaffold as Bioresorbable Drug-Eluting Vascular Graft

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Introduction

Arteriovenous grafts are used as an intervention for patients requiring repeated, long-term vascular access, such as those on dialysis. Improvements in synthetic grafts include using absorbable polymers for increased mechanical strength and reduced long-term issues. However, upon failure, graft placement can lead to thrombosis and intimal hyperplasia. Dipyridamole (DPA) has vasodilator and anti-platelet properties to inhibit intimal hyperplasia post graft placement. Incorporation of nanoparticles into vascular grafts allows for improved radiopacity and monitoring *in vivo*. This study aims to develop a bismuth nanoparticle (BiNP) and DPA loaded scaffold made of polycaprolactone (PCL) and polyethylene glycol (PEG). These scaffolds were tested for their efficacy as novel bioresorbable drug eluting vascular grafts.

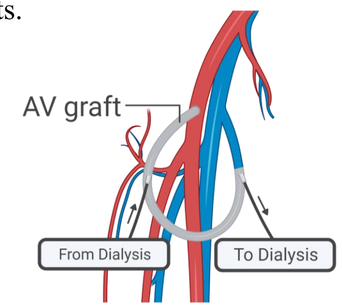

Fig. 1. AV graft showing connection of artery and vein for improved vascular access.

Methods

BiNPs were synthesized via the thermal decomposition method. Combinations of PCL (MW 80,000), PEG (MW 8,000), BiNP, and DPA were electrospun into 3 cm long scaffolds, and physiochemical properties were characterized. The amount of DPA and BiNP released from the grafts at each time point was quantified using UV-VIS spectroscopy and elemental analysis, respectively. Radiopacity was monitored weekly using Bruker-microCT, and Hounsfield units were quantified at each time point. The tensile strength of each scaffold was measured over a period of 6 weeks. EC-RF24 and MOVAS cell lines were used to test scaffold toxicity using alamarBlue assay. Scaffolds were surgically implanted in rats.

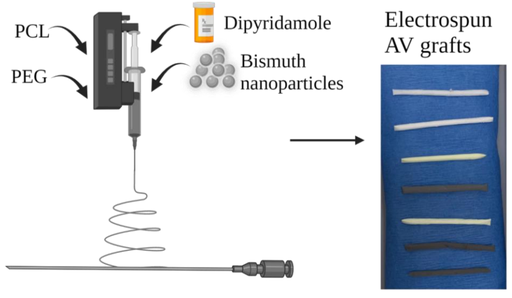

Fig. 2. Schema for electrospinning and photographs of the electrospun AV grafts.

Results

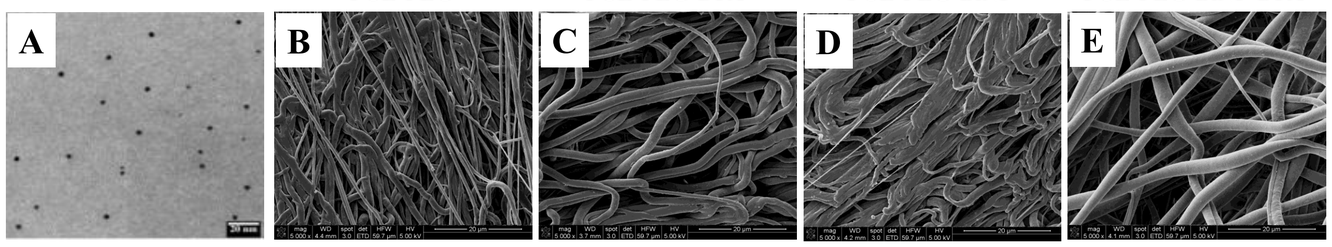

Fig. 1. Size and Morphology of synthesized BiNPs and electrospun scaffold. (A) TEM imaging of the synthesized BiNP. (B-E) SEM of the various polymeric scaffolds.

Table 1. Physio-chemical Properties of Scaffolds

	DPA (%)			Porosity (%)			
	Theoretical	Actual	Fiber Diameter (um)	Intrusion	Dimension	Max Stress (MPa)	Modulus of Elasticity (MPa)
PCL-PEG	0	0	1.56 ± 0.591	79.13 ± 2.42	80.26 ± 4.29	6.28 ± 2.77	3.63 ± 5.08
PCL-PEG-BiNP	0	0	1.92 ± 0.585	81.99 ± 6.80	86.43 ± 2.03	2.12 ± 0.42	4.40 ± 0.98
PCL-PEG-DPA	0.25	0.45	2.51 ± 0.827	74.81 ± 4.14	88.74 ± 0.91	7.65 ± 2.17	7.72 ± 2.65
PCL-PEG-BiNP-DPA	0.25	0.77	2.53 ± 0.644	80.02 ± 2.83	89.86 ± 0.49	3.42 ± 0.34	5.54 ± 3.08

Note: DPA-loaded grafts have a larger fiber diameter, and BiNP-loaded grafts have a lower tensile strength.

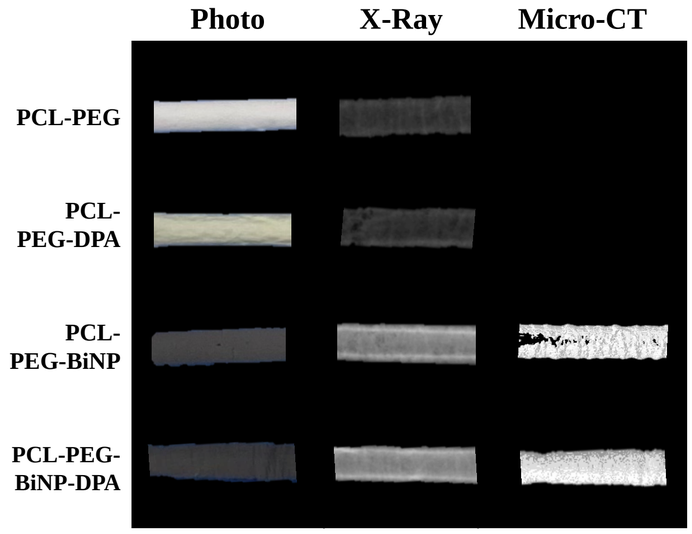

Fig. 2. Imaging of the electrospun scaffolds. Photographs, X-ray, and micro-CT images show radiopacity of scaffolds containing BiNP.

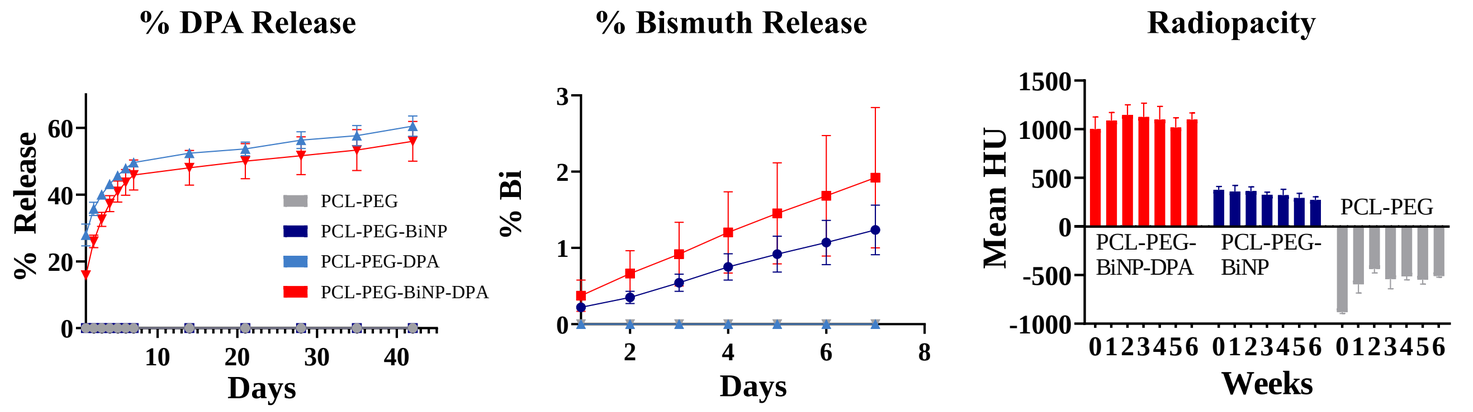

Fig. 3. Longitudinal Bi and DPA release, and radiopacity over time. DPA released rapidly within the first week and plateaued over the following weeks. Grafts loaded with both BiNP and DPA and spun with a 3:1 ratio of PCL:PEG had the highest radiopacity as measured by micro-CT. Bi release from grafts was slow, corresponding with radiopacity measurements.

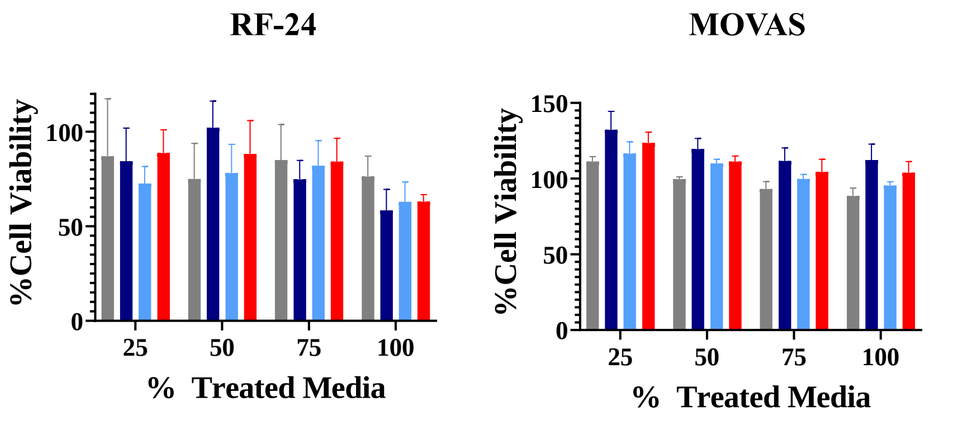

Fig. 4. Nanotoxicity study of loaded grafts. Cell viability of EC-RF24 and MOVAS cell lines measured by alamarBlue assay after 48h incubation in treated and untreated cell culture media.

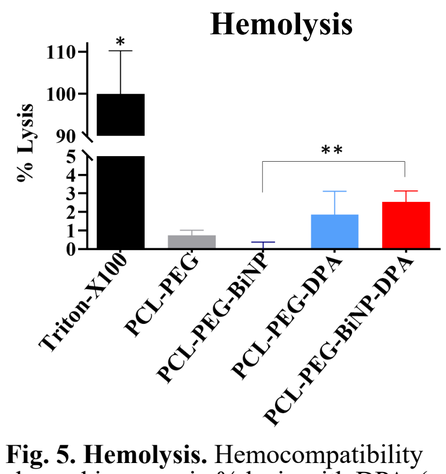

Fig. 5. Hemolysis. Hemocompatibility showed increase in % lysis with DPA ($p < 0.001$).

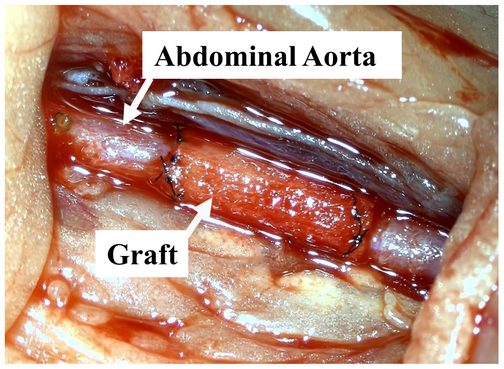

Fig. 6. *In vivo* graft placement in rat. PCL graft was sutured into place in rat abdominal aorta. Efficacy in terms of imaging and therapeutic response is currently on going.

Summary and Conclusions

- BiNP of 3.44 nm ± 0.59 nm size was successfully synthesized.
- Morphology of the polymeric scaffold changed in the presence of nanoparticle and drug, i.e. DPA loaded grafts have a bigger fiber diameter
- Up to 50% of the DPA was released during the first week, and release slowed down in succeeding weeks
- Increased radiopacity was observed in scaffold containing BiNP.
- Only about 1-2% of Bi are released, which correlates with CT imaging.
- Human epithelial cells and smooth muscle cells remained viable in the presence of BiNP and DPA treated media.
- The presence of DPA increased blood lysis by about 2%.

Future Research

In vivo rat studies involving microsurgical placement of these absorbable, radiopaque grafts to determine its safety and efficacy is currently ongoing. Different polymeric materials, drugs, and nanoparticles are also being explored.

Acknowledgements

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References

1) Lawson et al. *Nat Rev Nephrol* **16,** 586–602 (2020).
2) Kuji et al. *Kidney International* **69,** 2179-2185 (2006).
3) Murthy, Shashi. *Int J Nanomedicine* **2,** 129-141 (2007).