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Commentary
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Precision Elastin-Mimetic Electrospun Scaffolds for Aortic Root Reconstruction: Toward Regenerative, In-Situ Tissue Engineering

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ABSTRACT

Reconstruction of the aortic root demands materials that endure complex cyclic loading while preserving native hemodynamics. Current prosthetic and biologic conduits restore patency but do not recapitulate the elastin-dependent compliance and fatigue resistance intrinsic to the aortic root, contributing to valve dysfunction, progressive dilation, and long-term failure. Elastin-mimetic electrospun scaffolds, combining elastin-like polypeptides (ELPs) or elastin-based recombinamers with structural biodegradable polymers such as polycaprolactone (PCL), offer a rational path toward in-situ regeneration: immediate mechanical support, surface cues for endothelialization, and a degradative timetable that permits host extracellular matrix deposition. Here, we synthesize the current elastin and vascular tissue engineering literature, define quantitative design targets for aortic-root scaffolds, delineate a preclinical testing pipeline, and map the regulatory considerations required for clinical translation. We present two tables that map design levers to mechanical/biological criteria and preclinical endpoints with recommended assays and sample sizes. This perspective provides a concise, actionable roadmap for investigators and translational teams pursuing regenerative, elastin-mimetic solutions for aortic root reconstruction.

KEYWORDS: *aortic root; elastin; electrospinning; elastin-like polypeptide; tissue engineering; PCL; in-situ regeneration*

1 Clinical Need and Translational Opportunity:

Aortic root replacement is indicated for aneurysm, destructive endocarditis, and complex congenital pathology. Options include valve-sparing root repair, composite grafts with mechanical or bioprosthetic valves, and homografts. While lifesaving, these solutions trade biologic function for durability: mechanical devices require lifelong anticoagulation; bioprostheses calcify and degenerate; homografts are constrained by availability and variable durability (2). The aortic root's unique geometry and elastin-rich lamellar architecture produce tailored compliance and recoil that support valve leaflet coaptation and energy-efficient flow. Failure to reproduce this compliance creates stress concentrations, promotes remodeling, and predisposes to late dysfunction. A scaffold that reproduces elastin mechanics and bioactivity while allowing host remodeling could reduce reoperation rates and improve physiologic outcomes.

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2 Elastin Biology: Design Implications:

Elastin provides high extensibility (native elastic lamellae routinely allow >100% cyclic strain), near-instantaneous recoil, and exceptional fatigue life (>10^8–10^9 cycles) (1). Beyond mechanics, elastin and elastin-derived peptides modulate vascular smooth muscle cell (VSMC) phenotype and endothelial behaviors, signaling that guide constructive remodeling rather than fibrotic encapsulation. In adult humans, *de novo* elastogenesis is limited; therefore, scaffolds must either deliver elastin-mimetic cues that encourage organized matrix deposition or include slowly degrading elastin-mimetic polymers that substitute for lost function during remodeling (1–3). These biological realities drive three core scaffold requirements: (a) matched compliance and multiaxial mechanics, (b) biochemical motifs that promote endothelialization and regulated VSMC integration, and (c) degradation kinetics synchronized to neotissue formation.

3 Materials and Fabrication Strategy:

3.1 Elastin-mimetic Building Blocks:

Elastin-like polypeptides (ELPs) and elastin-based recombinamers are genetically encoded polymers that reproduce elastomeric behavior and allow sequence-level insertion of bioactive cues (3,4). Blending ELPs with structural, FDA-familiar biodegradable polymers, such as PCL, yields composite scaffolds in which the ELP fraction governs elasticity and surface bioactivity. At the same time, PCL maintains initial suture-pullout strength and dimensional stability (4,5).

3.2 Electrospinning and Architecture:

Electrospinning generates nanofibrous networks that mimic ECM organization and permit control over fiber diameter, alignment, porosity, and multilaminar organization, features crucial to reproducing the aortic wall's anisotropic mechanics (3,4). Design parameters targeted for aortic root scaffolds: fiber diameter 200–800 nm; aligned circumferential layers for tensile load transfer; pore sizes 10–50 μm to permit VSMC infiltration while limiting excessive dilation; and wall thickness 1–3 mm to approximate native wall thickness without impeding diffusion.

3.3 Surface Functionalization and Biochemical Cues:

RGD and other integrin-binding motifs, heparin-binding domains for growth factor retention, and controlled release of angiogenic cues (VEGF) can be integrated via co-electrospinning or surface coupling to accelerate endothelialization and guide quiescent VSMC phenotype (3,5). Crosslinking strategies must balance immediate mechanical stability with the need to permit cellular remodeling.

4 Quantitative Mechanical Targets and Hemodynamics:

A scaffold must match native aortic root multiaxial mechanics to preserve valve function and avoid stress concentrations. Practical target values to guide design and testing are:

- Circumferential tensile strength: 1–2 MPa
- Radial compliance: 5–10% per 100 mmHg
- Ultimate strain (failure): ≥150%
- Fatigue resistance: sustain >10^8 cycles without significant creep or loss of recoil

Preimplant optimization should couple mechanical testing (uniaxial, biaxial, cyclic fatigue) with computational fluid dynamics (CFD) to evaluate leaflet coaptation, flow separation, and shear stress distributions.

5 *In-vitro* and Preclinical Evaluation Roadmap:

A stepwise, hypothesis-driven pipeline accelerates safe translation:

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In vitro:

- Mechanical: uniaxial/biaxial tensile testing; cyclic fatigue; suture pull-out.
- Biological: cytotoxicity (ISO 10993-5), endothelial cell adhesion/migration, VSMC phenotype assays, elastogenesis markers (tropoelastin, LOX).
- Degradation: mass loss, mechanical retention, and chemical analysis of degradation products.

Small Animal (rodent/rabbit):

- Goals: biocompatibility, early infiltration, inflammatory profiling, and proof-of-concept elastin deposition.
- Endpoints: histology (H&E, elastin Van Gieson), IHC for VSMC/endothelial markers, and inflammatory cytokines.

Large Animal (sheep/pig):

- Goals: hemodynamic performance, valve competence, and long-term remodeling under physiologic pressures.
- Endpoints: serial echocardiography, MRI/CT for geometry and flow, explant histology, and mechanical testing of explanted tissue.

6 Design Levers and Preclinical Endpoints (Tables):

Table 1: Design Levers → Mechanical & Biologic Criteria:

Design Lever	Mechanical Target	Biological Criterion
Fiber alignment (circumferential)	Circumferential tensile 1–2 MPa	VSMC alignment; anisotropic ECM deposition
Fiber diameter (200–800 nm)	Balanced stiffness & porosity	Enables cell infiltration, limits thrombosis
ELP:PCL ratio (30–70%)	Tunable modulus 0.5–1.5 MPa	Temporary elastin function; supports remodeling
Crosslink density	Moderate	Permits cell-mediated remodeling
Surface functionalization (RGD, VEGF)	—	Enhanced endothelialization; reduced thrombosis

Table 2: Preclinical Endpoints, Assays, and Suggested Numbers:

Endpoint	Assay	Suggested (n)
Mechanical integrity	Tensile testing, cyclic fatigue	6–8
Cellular infiltration	Histology, IHC (CD31, α-SMA)	5–6
ECM deposition	Elastin/collagen stains; biochemical assays	5–6
Hemodynamic function	Echo, MRI flow quantification	4–6
Immunogenicity/inflammation	Cytokine panels, histology	5

7 Regulatory Considerations and Translational Milestones:

Scaffold development should integrate regulatory thinking from the outset. ISO 10993 biocompatibility testing (cytotoxicity, sensitization, genotoxicity/systemic toxicity) is required; ASTM standards for vascular grafts guide mechanical testing. Given the likely Class III designation for an aortic root implant, early engagement with the FDA/EMA is recommended. Sterility assurance, residual analysis, and characterization of degradation products are critical.

8 Clinical Translation Strategy:

Staged clinical translation: (a) first-in-human feasibility studies for patients unsuitable for conventional grafts; (b) randomized trials comparing valve-sparing outcomes; (c) long-term registry for durability and rare adverse events. Manufacturing scale-up, process validation, and reproducibility of ELP/PCL scaffolds are essential.

9. Limitations and Future Directions

Challenges include long-term elastogenesis, degradation kinetics, and large-scale manufacturing of recombinant ELPs. Future innovations may include bio-orthogonal crosslinking, hybrid 3D printing/electrospinning, and gene-activated scaffolds to upregulate elastin synthesis.

Conclusion:

Electrospun elastin-mimetic scaffolds, rationally designed to meet measurable mechanical targets, provide bioactive cues and include a clear preclinical/regulatory roadmap, and represent a viable strategy for regenerative aortic root reconstruction. Such scaffolds can restore native compliance, support valve function, and promote durable, in-situ tissue regeneration.

Conflict of Interest:

None

Ethical Consideration:

None

Declaration of AI Use:

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