Carbon®

Novel Bioabsorbable Implants with Elastomeric Properties Using Carbon's Digital Light Synthesis Platform

Bioabsorbable materials are a well-established technology found in a variety of implantable medical devices employed in procedures involving both hard and soft tissues. Implants are used when it is desirable to provide mechanical support over a sufficient duration to allow the body to reestablish natural tissues and function. Given their ability to be placed in a target tissue, they have also been used for localized therapeutic delivery.

Background

Traditional manufacturing methods, such as injection and compression molding, yield medical devices limited by both the intrinsic properties of available bioabsorbable materials as well as geometries amenable to these molding techniques. Customized implants, for example, are either impractical or prohibitively expensive using traditional manufacturing methods. 3D printing addresses these shortcomings by enabling the facile production of customized medical devices and implants.[1] Additionally, complex geometries such as lattices, which enable advantageous new device structures, are only possible using additive manufacturing.

Throughout the last decade, there have been several examples of 3D printed materials for biomedical applications including stents,[2–5] dental implants[6] and prosthetics.[7] Advancements in 3D printing technology have also accelerated the development of bioabsorbable materials for the rapid production of customized implantable devices for tissue support and healing. Most applications using bioabsorbable materials are either rigid, high modulus devices such as sutures[8] and fasteners[9], or woven structures that achieve flexibility and larger spatial coverage.[10] There are few examples of commercial elastomeric bioabsorbables, although much work has been done in the academic sector.[3,11]

Bioabsorbable polyesters, such as polycaprolactone, poly(lactic acid) and polyglycolide, are among the most widely studied polymers for biomedical applications. Known for their tunable degradation times, tunable mechanical properties and biocompatibility, these polymer backbones are great candidates for building a platform of oligomers for bioabsorbable, 3D-printable resins. Lactone-based polymers are easily synthesized using ring opening polymerization. Control over initiator choice, monomer feed ratio, and molecular weight allows for variation in polymer architecture, degradation rate, functionality, and mechanical properties. These polymers rely on hydrolysis and, in some cases, enzymatic function to degrade the material to safe, low molecular weight compounds. Degradation rates are slowed by adding more hydrophobic monomers and/or increasing the crystalline fraction. A range of mechanical properties can be achieved with a mix of semi-crystalline and amorphous microstructure, tunable through copolymerization.[12,13]

Carbon's Contribution

At Carbon, we recently developed a platform of photopolymerizable bioabsorbable elastomeric (BE) resins based on tunable methacrylate-terminated polyester oligomers (ATPEs) (Figure 1).
A combination of copolymer chemistries and a mix of linear and branched topologies provides a range of compositions enabling a broad spectrum of degradation rates without sacrificing initial mechanical properties. In vitro and in vivo studies have demonstrated the required tissue tolerance and desirable healing responses for an implantable device.

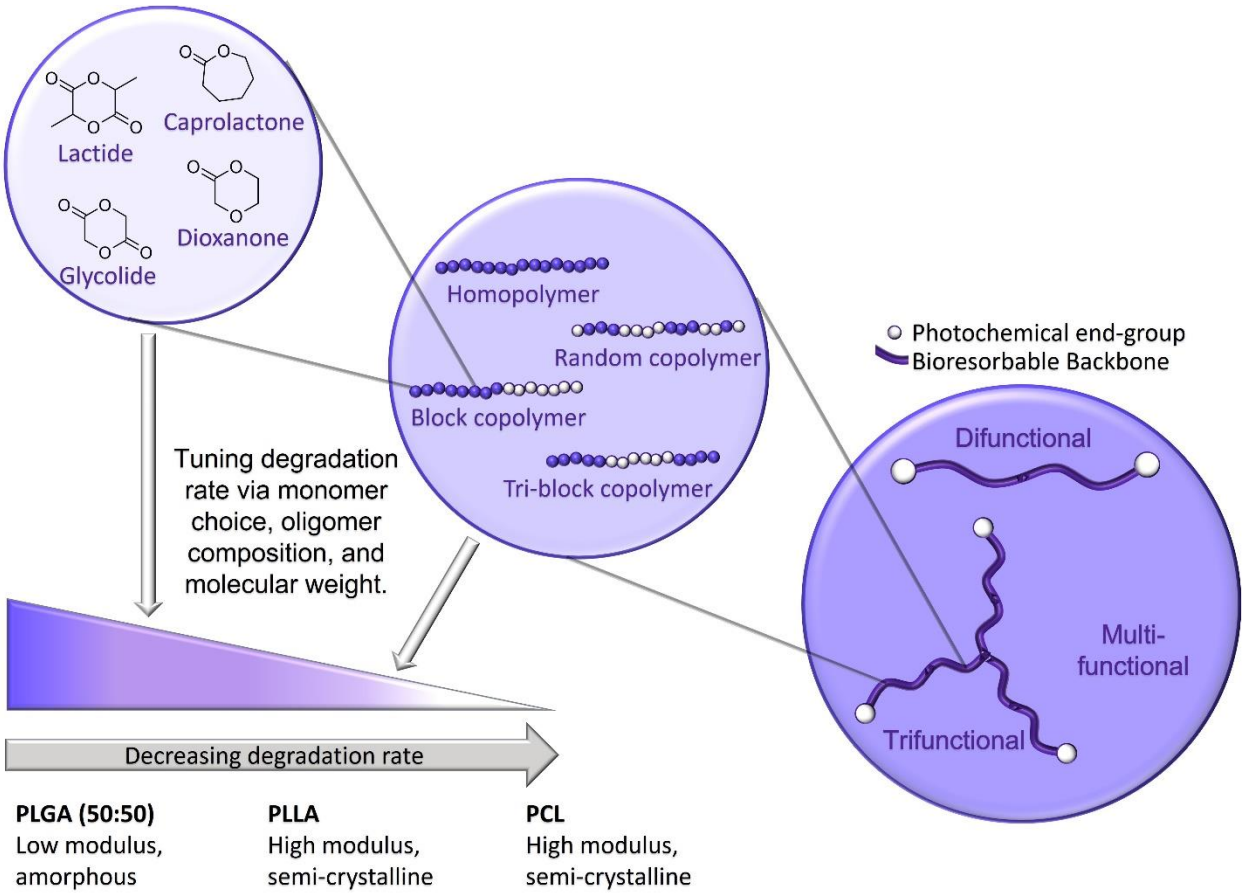

Figure 1. ATPEs are the main component of Carbon's bioabsorbable resin platform. The ATPEs are linear or branched, methacrylate-terminated polyester oligomers that vary in molecular weight, oligomer composition, and monomer backbone which allows for tunability of degradation rate without sacrificing elastomeric properties.

ATPEs are formulated with a range of diluents, a photoinitiator, and processing aids, to yield low viscosity BE resins which are ideal for printing with DLSTM technology on the Carbon® M-Series Printers. Printed parts have glass transition temperatures (T_g) below body temperature and display minimal hysteresis, high elongation at break and a range of modulus retention and total absorption times in vivo as indicated in Table 1.

Table 1. Resin and printed part properties of BE resins.

Property	BE Resin
Resin Viscosity at Room Temperature	2500 cP
Tensile Modulus	5 MPa
Elongation at break	>200%
T_g	14 to 25 °C
Accelerated Mass Loss at 14 days (60 °C, PBS pH 7.4, buffer change at pH <7.1)	15 to 60% mass loss
Modulus Retention at 28 days (37 C, PBS pH 7.4, buffer change at pH <7.1)	22 to 60 % modulus retention
Total Absorption Time (in vivo)	≥180 days (degradation observed at 90 and 120 days)

Carbon has also developed a proprietary processing workflow to generate devices suitable for implantation. This includes washing, post-curing, and sterilization of printed parts (Figure 2).

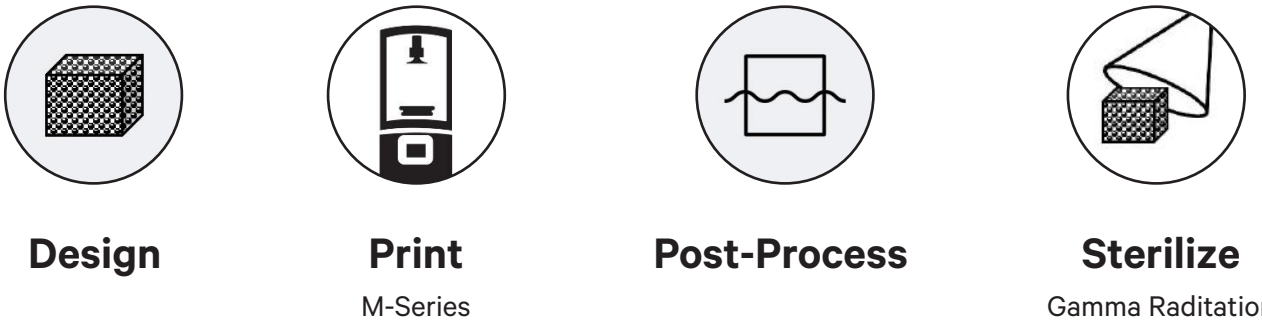

Figure 2. Complete workflow of the BE resin platform includes design, printing on the Carbon M Series Printer, post-processing, and sterilization.

The mechanical properties of the BE geometries pre- and post-gamma sterilization were studied using dynamic mechanical analysis. Temperature sweeps (RSA-G2, 1Hz) resulted in no significant changes in the tan delta and storage modulus before and after sterilization (Figure 3a), indicating there is minimal chain scission or degradation of the polyester materials when exposed to gamma radiation at this dose. It is crucial that new materials for medical devices are capable of sterilization. There are various methods commonly used for sterilization purposes, such as Gamma sterilization.

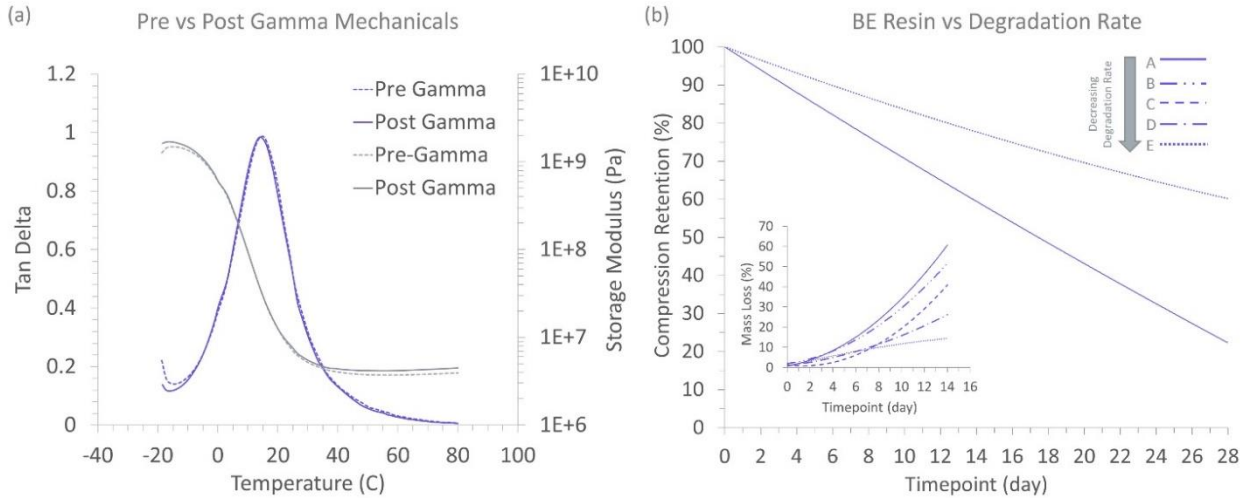

Figure 3. (a) Temperature sweeps on the RSA-G2 (1Hz) were conducted pre and post gamma sterilization (1 dose, 25 kGy) to determine if the BE materials could withstand this sterilization method. No significant change in tan delta and storage modulus was observed for these resins. (b) The fastest and slowest degrading BE resins were studied in vitro for compression modulus retention over 28 days in biological conditions (37°C, pH 7.4). Compression modulus was tested at 0,3,7,14, and 28 days (n=3) to determine modulus retention over time. (b inlay) Mass loss degradation studies were conducted for the entire BE resin family in accelerated conditions in vitro (60°C, pH 7.4). Mass loss ranged from 14 to 60% across the entire BE family.

Degradation rate is primarily driven by the ATPE polyester backbone which is the major component in BE resins. Tunable degradation rates are achieved by altering the ATPE composition and adjusting the ratio of various ATPEs in the formulation. The results of the in vitro degradation studies are shown in Figure 3b. Compression modulus retention was studied over 28 days in vitro for the fastest (resin A) and slowest (resin E) absorbing resins in biological conditions. Data was collected at various timepoints throughout the 28-day study. Both resins exhibit a linear decrease in compression modulus over time, with the fastest degradation rate resulting in 22% compression modulus retention, compared to 60% compression modulus retention for the slowest degrading BE. Similarly, the entire BE resin platform (resin A through E) was studied in accelerated mass loss conditions over 14 days (Figure 3b inlay). A decreasing trend in degradation rate from BE resin A to E was Varying ratios of multiple ATPEs in BE formulations results in a clear trend in decreasing degradation rate from resin A to resin E as expected.

Leveraging its technology at the intersection of materials, hardware and software, Carbon has demonstrated that a variety of lattice structures with a range of mechanical responses are achieved with the BE resin platform. Both surface and strut-based lattices have been printed on the Carbon M-Series Printers with high resolution and feature sizes as small as 180 µm (Figure 4a). The ability to print these BE resins in a variety of lattice structures, enables yet another lever for tuning degradation time and mechanical properties of the printed construct. Figure 4b depicts the range of compression profiles observed the same BE resin printed in various lattice structures. Wall thickness and lattice geometry play a critical role in stiffness and densification of the final printed part. Additionally, with increasing wall thickness, a decrease in degradation rate will likely be observed due to the decreased surface area of the eroding structure.

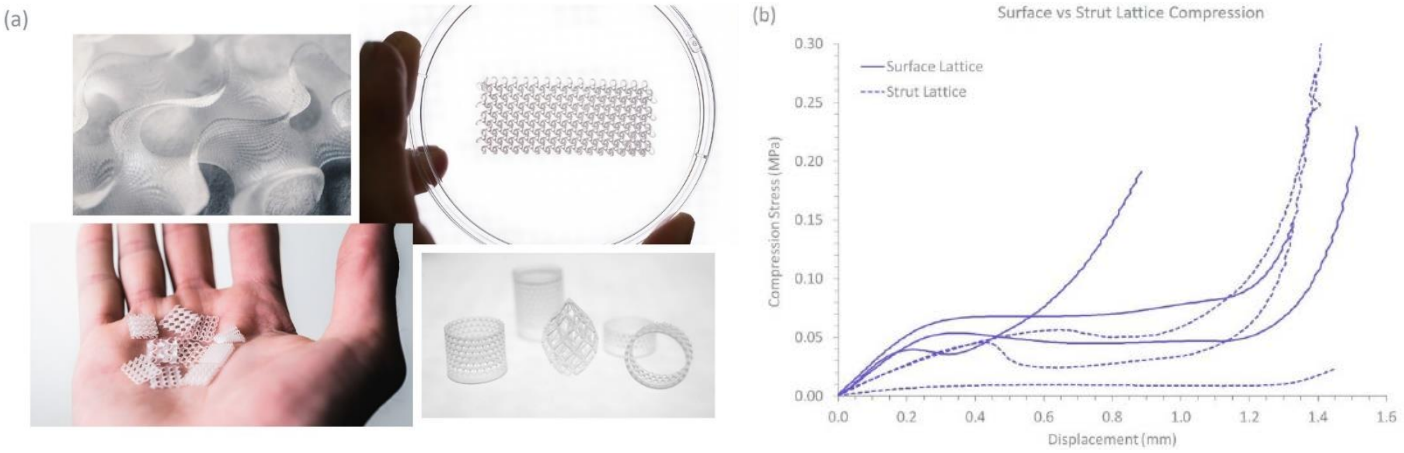

Figure 4. (a) Surface and strut-based lattice geometries have been printed on the Carbon M2 series with high resolution. Parts pictured were designed with wall thicknesses ~180-250 µm wide. (b) Using DLS technology, Carbon can print a variety of strut-based and surface lattices to obtain various compression profiles using the same BE resin.

To date, limited information of full degradation biocompatibility tests in vivo for photoinitiated, bioabsorbable systems has been reported. To assess the biocompatibility and degradation rate of the BE resin platform, subcutaneous rabbit implants were performed as compared to a commercially available woven bioabsorbable control (Seamguard® bioabsorbable) by North American Science Associates, Inc. ("NAMSA"). Surface lattices (5 mm x 10 mm x 2.15 mm) were prepared via the workflow in Figure 2. Samples were gamma sterilized and remained in the nitrogen-sealed pouches until implantation. Macroscopic and microscopic assessment of the surrounding tissue was performed at 2, 4, 8, 17, and 26 weeks post-implantation. A range of degradation profiles were observed with degradation starting as early as 8 weeks and persisting through 26 weeks. Histological assessment and scoring were performed at Translation Pathology Associates following ISO-10993-6 test methods for the assessment of the local effects after implantation of biomaterials intended for use in medical devices.

Figure 5 shows representative histological images for the complete degradation time series of BE resin A and E, the fastest and slowest degrading resins, respectively. All BE resins were classified as non-irritants and no tissue necrosis was observed through 26 weeks. Healthy tissue infiltration and blood vessel formation suggests that the BE resins are suitable for the future of additive manufacturing applications in bioabsorbable implants.

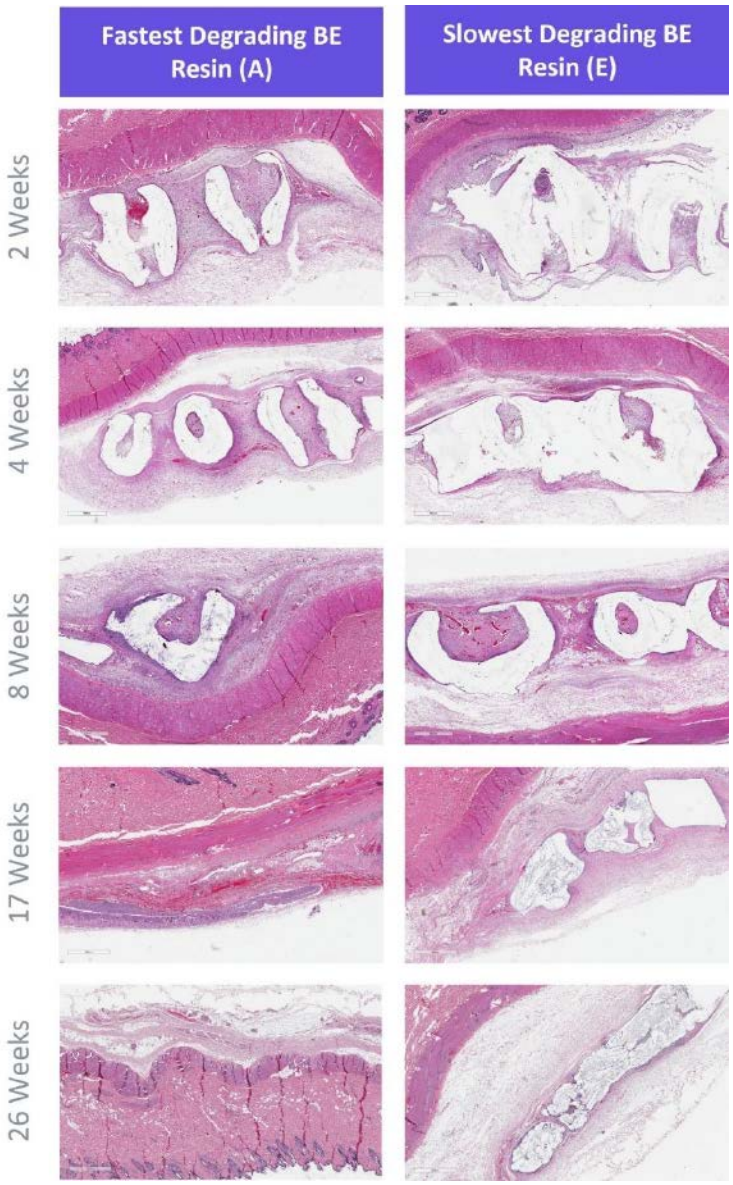

Figure 5. Microscopic histological images of the fastest and slowest degrading BE resin constructs depict the healthy tissue that is infiltrating into the lattice structure as the material undergoes hydrolysis in vivo. BE resins were deemed non-irritants through 26 weeks and range degradation times were observed. At 26 weeks, the fastest degrading resin (A) shows complete absorption, while the resin E lattice is easily visualized, with fragmentation occurring.

Conclusion

Polyester-based bioabsorbable materials have been heavily studied over the last several decades for applications in tissue engineering and tissue support. Despite the many examples of bioabsorbable materials that exist in the medical device industry today, there are few examples of 3D printed elastomeric bioabsorbables. Carbon has developed a platform of bioabsorbable resins that are capable of printing customized, complex, and high-resolution, elastomeric lattice structures. Our BE resins offer tunable degradation, compatibility with gamma sterilization, and excellent biocompatibility through 180 days of in vivo degradation making them prime candidates for soft tissue reconstruction and support applications. We anticipate that these materials, combined with new structural capabilities enabled by additive manufacturing, will usher in a new wave of bioabsorbable implantable devices that greatly expand and improve treatment possibilities for a wide variety of patient needs.

Talk to a Carbon BE expert about your application at sales@carbon3d.com.

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References

(1) Ghosh, U.; Ning, S.; Wang, Y.; Kong, Y. L. Addressing Unmet Clinical Needs with 3D Printing Technologies. *Advanced Healthcare Materials* 2018, 7 (17), 1800417. https://doi.org/10.1002/adhm.201800417.

(2) Wang, C.; Zhang, L.; Fang, Y.; Sun, W. Design, Characterization, and 3D Printing of Cardiovascular Stents with Zero Poisson's Ratio in Longitudinal Deformation. *Engineering* 2021, 7 (7), 979–990. https://doi.org/10.1016/j.eng.2020.02.013.

(3) Yeazel, T. R.; Becker, M. L. Advancing Toward 3D Printing of Bioresorbable Shape Memory Polymer Stents. *Biomacromolecules* 2020, 21 (10), 3957–3965. https://doi.org/10.1021/acs.biomac.0c01082.

(4) Guerra, A.; Cano, P.; Rabionet, M.; Puig, T.; Ciurana, J. 3D-Printed PCL/PLA Composite Stents: Towards a New Solution to Cardiovascular Problems. *Materials* 2018, 11 (9), 1679. https://doi.org/10.3390/ma11091679.

(5) Verheye, S.; Ormiston, J. A.; Stewart, J.; Webster, M.; Sanidas, E.; Costa, R.; Costa, J. R.; Chamie, D.; Abizaid, A. S.; Pinto, I.; Morrison, L.; Toyloy, S.; Bhat, V.; Yan, J.; Abizaid, A. A Next-Generation Bioresorbable Coronary Scaffold System: From Bench to First Clinical Evaluation. *JACC: Cardiovascular Interventions* 2014, 7 (1), 89–99. https://doi.org/10.1016/j.jcin.2013.07.007.

(6) Sheela, U. B.; Usha, P. G.; Joseph, M. M.; Melo, J. S.; Thankappan Nair, S. T.; Tripathi, A. 3D Printing in Dental Implants. In 3D *Printing in Medicine and Surgery*; Elsevier, 2021; pp 83–104. https://doi.org/10.1016/B978-0-08-102542-0.00007-5.

(7) Manero, A.; Smith, P.; Sparkman, J.; Dombrowski, M.; Courbin, D.; Kester, A.; Womack, I.; Chi, A. Implementation of 3D Printing Technology in the Field of Prosthetics: Past, Present, and Future. *International Journal of Environmental Research and Public Health* 2019, 16 (9), 1641. https://doi.org/10.3390/ijerph16091641.

(8) Scott Taylor, M.; Shalaby, S. W. Sutures. In *Biomaterials Science*; Elsevier, 2013; pp 1010–1024. https://doi.org/10.1016/B978-0-08-087780-8.00087-5.

(9) Ignatius, A. A.; Augat, P.; Ohnmacht, M.; Pokinskyj, P.; Kock, H.-J.; Claes, L. E. A New Bioresorbable Polymer for Screw Augmentation in the Osteosynthesis of Osteoporotic Cancellous Bone: A Biomechanical Evaluation. *Journal of Biomedical Materials Research* 2001, 58 (3), 254–260. https://doi.org/10.1002/1097-4636(2001)58:3<254::AID- JBM1014>3.0.CO;2-A.

(10) McMahan, S.; Taylor, A.; Copeland, K. M.; Pan, Z.; Liao, J.; Hong, Y. Current Advances in Biodegradable Synthetic Polymer Based Cardiac Patches. *Journal of Biomedical Materials Research Part A* 2020, 108 (4), 972–983. https://doi.org/10.1002/jbm.a.36874.

(11) Worch, J. C.; Weems, A. C.; Yu, J.; Arno, M. C.; Wilks, T. R.; Huckstepp, R. T. R.; O'Reilly, R. K.; Becker, M. L.; Dove, A. P. Elastomeric Polyamide Biomaterials with Stereochemically Tuneable Mechanical Properties and Shape Memory. *Nature Communications* 2020, 11 (1), 3250. https://doi.org/10.1038/s41467-020-16945-8.

(12) Choi, S. H.; Park, T. G. Synthesis and Characterization of Elastic PLGA/PCL/PLGA Tri- Block Copolymers. Journal of Biomaterials Science, *Polymer Edition* 2002, 13 (10), 1163–1173. https://doi.org/10.1163/156856202320813864.

(13) Woodard, L. N.; Grunlan, M. A. Hydrolytic Degradation of PCL–PLLA Semi-IPNs Exhibiting Rapid, Tunable Degradation. *ACS Biomaterials Science & Engineering* 2019, 5 (2), 498–508. https://doi.org/10.1021/acsbiomaterials.8b01135.

