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A Versatile Synthetic Platform for a Wide Range of Functionalized Biomaterials

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The introduction of functionalities to synthetic biomaterials represents a major direction and a significant challenge in biomedical engineering. A synthetic platform using novel acid-induced epoxide ring-opening polymerization promoted by a newly designed catalyst to produce a variety of biodegradable and functionalized biomaterials is reported. The polymerization proceeds smoothly in the presence of functional groups including alkenyl, aromatic, ether, ester, and free hydroxyl groups. The functionalities of the resultant biomaterials can be further enriched using many post-functionalization methods. This platform yields biomaterials with a wide range of hydrophilicity, crystallinity, charge, mechanical properties, and cell interactions. This platform for functionalized biomaterials is simple, versatile, and can be easily adapted to specific cell types and tissues of interest.

1. Introduction

Biomaterials play a central role in medical device and regenerative medicine and will continue to make major impacts on healthcare.[1–3] Active research in biomaterials is shifting from biostable to biodegradable materials.[4–6] Convergence of biodegradability and functionalities including unique mechanical properties and bioactivity is a major direction of new generation biomaterials.[2–5] Among various synthetic biodegradable materials, polyester is perhaps the largest class with classic examples such as polylactide and polycaprolactone.[5–8] However, synthetic polymers including polyesters are usually biologically inert and lack functionalities.[5,7] Introduction of functional groups to a polymer and subsequent functionalization provide an efficient way to tailor the properties of polymers such as hydrophilicity, crystallinity, elasticity, and bioactivity. Thus, the functionalized polyesters hold great potential for biomedical applications compared to their non-functionalized counterparts.[9–13]

Despite significant advances, synthesis of functionalized polyesters is still a challenge.[9,11,12] There are two major synthetic strategies: 1) polymerization of functionalized monomers and 2) post-polymerization functionalization. Polymerization of functionalized monomers provides relatively precise control of the final products and has been widely used. Biologically relevant functional groups that are ubiquitious in biological systems, such as hydroxyl, carboxyl, and amino groups, can modulate cell behaviors and are amenable to various modifications via biodegradable bonds such as ester, amide, and glycosidic bonds.[14–16] Thus, hydroxyl, carboxyl, and amino are the preferred functional groups. However, due to their high reactivities, careful protection and deprotection steps are usually required.[9,10,13,16–18] The extra steps increase the burden on time, labor, and cost and decrease the overall yield. One good alternative to avoid protection and deprotection is to first introduce relative stable functional groups such as alkynyl, alkenyl, carbonyl, halide, and azido followed by post-polymerization transformations such as click and Michael addition reactions to provide polyesters with desired functionalities.[9,19–21] However, functionalized monomers either with protected active functional groups or with relative stable functional groups are usually not readily available and need to be prepared by multistep synthesis.[9,11,16,18–21] In addition, post-polymerization reactions including deprotections and functional group transformations are usually required to produce biologically relevant functionalities. All of this usually compromises the overall efficiency and yield. Post-polymerization functionalization is relatively straightforward.[9] However, harsh reaction conditions such as lithium diisopropylamide are usually needed to generate reactive sites in relatively inert unfunctionalized polymer chain. These reactions are difficult to control and may result in undesired side reactions such as chain degradation and racemization.[9,10,22] Thus, the use of post-polymerization functionalization is somewhat limited. Besides chemical methods, enzymatic polymerization provides a relative simple way to prepare functionalized polyesters. Its major drawback is the limited scope of substrates.[13,23–26] In light of these facts, new synthetic strategies of functionalized polyesters are highly desirable.

We set out to address the critical barrier in the synthesis of functionalized polyesters by designing a simple and versatile synthetic platform that yields functionalized polyesters with diverse physical, chemical, mechanical, and biological properties (**Figure 1**, **Table 1**). The key of this platform technology is acid-induced epoxide ring-opening polymerization, where epoxy groups serve as both functional groups for polymerization and precursors of the hydroxyl groups. A wide range of monomers, dicarboxylic acids and diepoxides, are commercially available or

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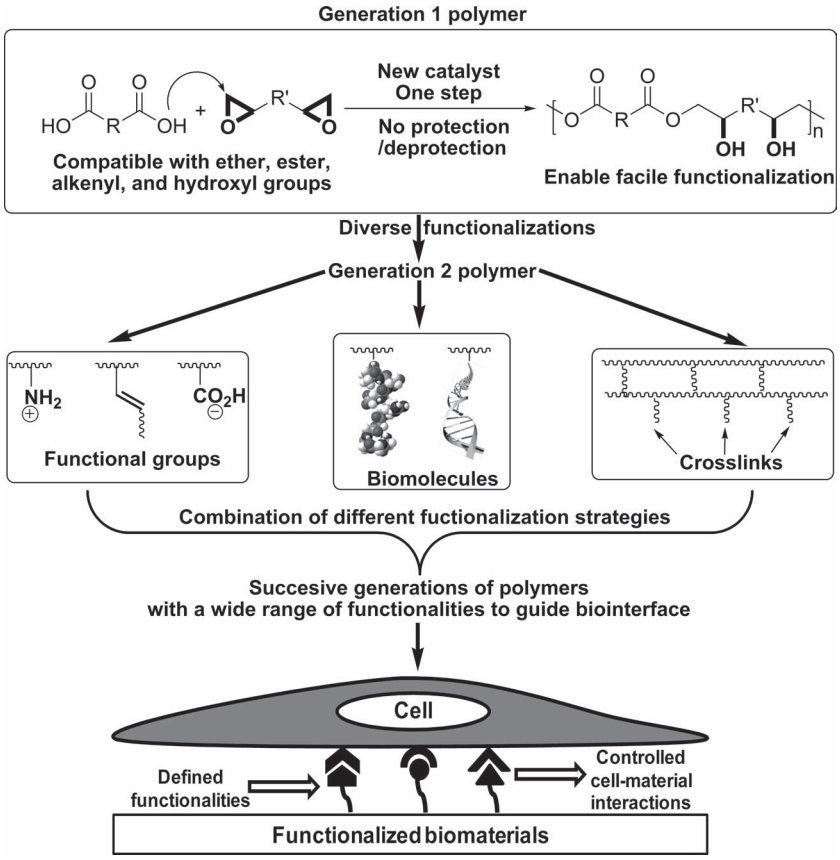

Figure 1. A simple synthetic platform of biomaterials with a wide range of functionalities that can offer fine control of cell-material interactions.

can be readily prepared. The polyester backbone and the free hydroxyl groups form in one step without protection and deprotection (generation 1 polymers, Table 1, 1A–1H), which are required for almost all existing chemical synthesis of hydroxyl functionalized polyesters and greatly compromise the efficiency and yield.[13,27] We chose hydroxyl group as the stepping stone for further functionalization because of its well-established modification methods.[28] Transformations of the hydroxyl functional groups lead to generation 2 polymers (**Figure 2**, 2A–2I) that greatly broaden the range of functional groups. Repeating this process can produce a wide range of materials with intricate structures in successive generations of polymers. The functional groups in this family of polymers can conjugate biomolecules or form crosslinks to produce functionalized polymeric materials. Combining these functionalizations can program polymers with defined structures and consequently tailored biointerfaces. To the best of our knowledge, this level of simplicity and versatility is uncommon; most of the reported synthetic strategies for functionalized polyesters require elaborate preparation of specially functionalized monomers and/or protection and deprotection.

2. Results and Discussion

2.1. Acid-Induced Epoxide Ring-Opening Polymerization

The proposed acid-induced epoxide ring-opening polymerization is applicable to a wide range of substrates that can be short or long chain, linear or cyclic, aliphatic or aromatic (Table 1). The monomers are commercially available or easily prepared in one step. A potential challenge to overcome in this synthetic route is the side reaction between the epoxy groups of the starting material and the hydroxyl groups in the product that will lead to undesired crosslinking.[29] Various quaternary onium salts have been developed to catalyze the polyaddition reactions between cylic ethers and carboxylic acids. However, the reactions usually need high amount of catalyst, high temperature, or long reaction time.[29–32] Accordingly, we designed bis(tetrabutylammonium) sebacate (TBAS), which is simultaneously a catalyst and a reagent that can induce the polycondensation reaction. We optimized the reaction conditions using polymer **1C** as a model compound (see **Table 2** for typical conditions). The design and proposed mechanism of this polymerization have been detailed in another manuscript.[33] Briefly, the tetrabutylammonium cation of TBAS serves as catalyst to facilitate the epoxide ring-opening reactions and the sebacate anion of TBAS induces the polymerization reaction by attacking the epoxy groups. The resultant alkoxy group will extract the protons from carboxylic acid groups and regenerate the carboxylate, which serves as the active species in the polymerization. The potential side reaction between the epoxy group and hydroxyl group is suppressed in the presence of carboxylate, which has higher nucleophilicity than neutral hydroxyl group. TBAS was readily prepared by the neutralization of tetrabutylammonium hydroxide with sebacic acid. The polymerization proceeded with good yield (75–99%) and produced polymers with a number-average molecular weight (M_n) between 10.6 and

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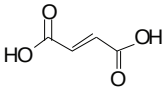
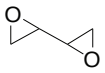
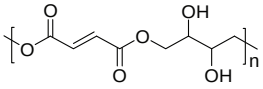
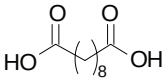
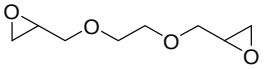
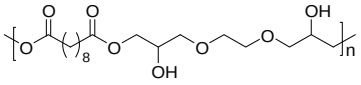
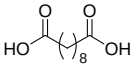
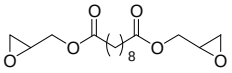
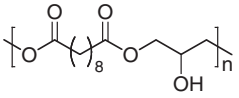
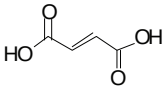
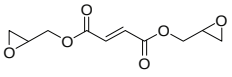
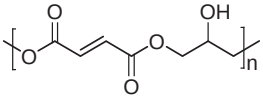
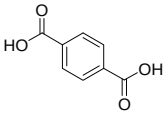
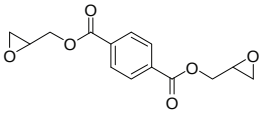
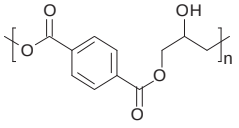
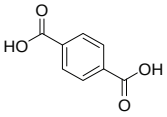
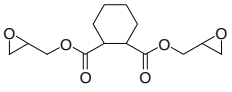
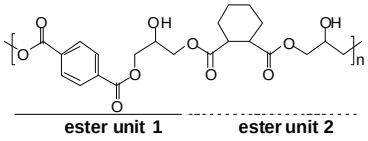
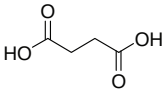
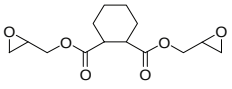
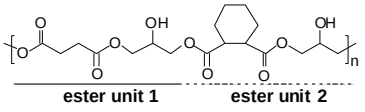
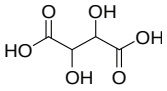
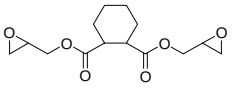
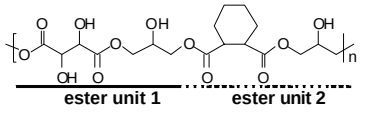
Table 1. Acid-induced epoxide ring-opening polymerization: a simple method to produce polyesters with free hydroxyl and other functional groups. The reactions were performed in *N*,*N*-dimethylformamide (DMF) at 100 °C (except *1A* at 85 °C), in a N_2 atmosphere using 0.6 mol% catalyst bis(tetrabutylammonium) sebacate for 26 h.

Diacid	Diepoxide		Generation 1 polymers	M_n [kD]		Yield [%]
		**1A**		25.1	1.6	99
		**1B**		12.1	1.1	75
		**1C**		73.3	1.4	87
		**1D**		10.6	1.7	99
		**1E**		23.8	2.5	94
		**1F**	 ester unit 1 ester unit 2	12.8	1.9	99
		**1G**	 ester unit 1 ester unit 2	12.5	1.6	98
		**1H**	 ester unit 1 ester unit 2	75.4	3.5	81

75.4 kD and polydispersity index (PDI) from 1.1 to 3.5. The presence of active species in the polymerization could account for the relatively high molecular weight and narrow PDI observed in this study compared to typical step-growth polymerization. In addition, the purification step would lead to fractionation of the polymers that also result in higher molecular weight and narrower PDI of the polymers. This synthetic platform overcomes several typical drawbacks of existing synthetic strategies to functionalized polyesters: toxic metal catalyst, complicated monomer preparations, and elaborate protection and deprotection manipulations.[13,17,27] Its simplicity is comparable to enzyme-catalyzed synthesis, but this platform provides a wider scope of substrate, higher molecular weight, and narrower PDI.[13,25,26,34] TBAS has excellent cytocompatibility,[33] a feature that makes this synthetic strategy especially attractive for biomedical applications in which the toxicity of the residual catalyst is a concern.[9]

The polymerization is compatible with at least four functional groups: hydroxyl, alkenyl, ester, and ether (Table 1), which is broader than other chemical polyesterification methods.[13] The compatibility with ester groups enables the synthesis of copolyester **1F**, a combination of poly(terephthaloyl diglyceride) and poly(1,2-cyclohexanediacyl diglyceride) in an alternating sequence. Employing different diacids to vary the structural units produces a family of repeating sequence copolymers (**1F–1H**). This provides a simple solution to a significant challenge in polymer synthesis: controlling the polymer sequence.[35–37] These sequence-controlled copolymers may show unusual properties compared to random copolymers.[35] The compatibility with alkenyl groups allows the synthesis of **1D**, a poly(propylene fumarate) functionalized by hydroxyl groups. Poly(propylene fumarate) is widely used in tissue engineering and drug delivery and has been functionalized by peptides through the alkenyl groups.[38,39] Mild polymerization conditions reserve the alkenyl groups in **1D** without using crosslinking inhibitors.[38] On the other hand, numerous hydroxyl groups offers additional routes to functionalize poly(propylene fumarate).

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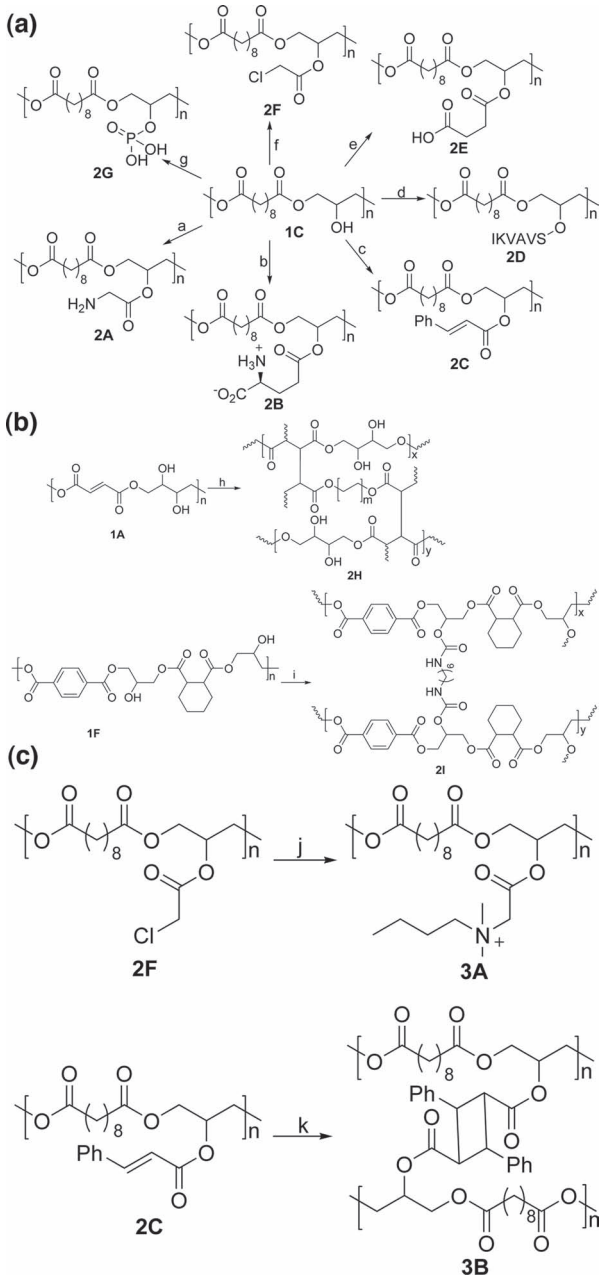

Figure 2. Diverse functionalizations of the polymers. a) Modification of the free hydroxyl groups in representative generation 1 polymers **1C**. b) Polymeric networks made by crosslinking of generation 1 polymers, another efficient method of functionalization. c) Two examples of further functionalizations of generation 2 polymers either by linear conjugation or crosslinking. Reagents and conditions: a) i. Boc-Gly-OH (Boc, *tert*-butyloxycarbonyl; Gly, glycine), *N*,*N*′-dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), CH_2Cl_2, room temperature (rt), 18 h; ii. CF_3CO_2H, rt, 0.5 h. b) i. Boc-Glu-O*t*Bu (Glu, glutamic acid; *t*Bu, *tert*-butyl), DCC, DMAP, CH_2Cl_2, rt, 17 h; ii. CF_3CO_2H, rt, 0.5 h. c) *Trans*-cinnamic acid, DCC, DMAP, CH_2Cl_2, rt, 18.5 h. d) i. Boc-IK(Boc)VAVS(*t*Bu)-OH (I, isoleucine; K, lysine; V, valine; A, alanine; S, serine), DCC, DMAP, DMF, rt, 68 h; ii. CF_3CO_2H, rt, 0.25 h. e) Succinic anhydride, DMF, 100 °C, 1 h. f) $ClCH_2COCl$, pyridine, CH_2Cl_2, –15 °C, 3 h. g) $POCl_3$, –15 °C, 2.5 h. h) Low molecular weight **1A** (Table 3, entry 1), poly(ethylene glycol) diacrylate, Igracure 2959, 365 nm UV, 0.4 h. i) 1,6-Hexyldiisocyanate, 140 °C for 30 h. j) $CH_3COOCH_2CH_2N(CH_3)_2$, acetone, rt, 17 h. k) 365 nm UV.

Table 2. Efficient functionalization of polymer **1C.**

Starting material **1C**		Product				Functionalization%	
M_n [kD]	PDI	Polymer	M_n [kD]	PDI	Yield [%]	Theoretical[d]	Experimental[e]
7.5	1.1	**2A**[a]	10.8	1.2	83	100	95
11.7	1.6	**2B**[b]	15.2	1.7	74	100	90
11.7	1.6	**2C**[b]	14.6	3.9	84	100	70
7.5	1.1	**2D**[a]	14.2	1.8	81	30	25
73.3	1.4	**2E**[c]	103.1	1.3	92	100	100
73.3	1.4	**2F**[c]	96.3	2.4	91	100	100
7.5	1.1	**2G**[a]	6.3	2.0	99	50	18[f]
73.3	1.4	**3A**[c]	109.7	1.2	86	100	100

Polymer **1C** was synthesized at: [a]70 °C for 26 h; [b]75 °C for 24 h; [c]100 °C for 26 h; [d]The theoretical percentage conversion from hydroxyl groups to corresponding functional groups according to the feed ratio of the reagents; [e]The actual percentage of the conversion calculated by analyzing the relative integrations in ^{1}H NMR spectra. The reaction conditions were not optimized; [f]According to inductively coupled plasma atomic emission spectroscopy analysis of phosphorus.

In addition, the polymerization could be efficiently controlled by altering reaction conditions. This provided an additional way to modulate the polymer properties (**Table 3**). As a proof of principle, we synthesized **1A** in relatively low temperature and short time (Table 3, entry 1). The resultant low molecular weight **1A** showed dramatically different properties from aforementioned **1A** (Table 3, entry 2), which had a high glass transition temperature (T_g) and did not dissovle in water. Thus it might be used a plastic biomaterial. The low molecular weight **1A** became water soluble and could form hydrogel after crosslinking (Figure 2B, polymer **2H**).

2.2. Facile and Versatile Post-Polymerization Functionalization

Organic transformation of the functional groups greatly enriched the chemical diversity of the resultant polymers. As a proof of principle, we used **1C** to illustrate the transformations of the hydroxyl groups (Figure 2), which reacted smoothly with various substrates including carboxylic acids, acyl chlorides, and anhydrides to yield biomaterials with diverse functional groups including primary amines (**2A**, **2B**, **2D**), zwitterions (**2B**), cinnammyl groups (**2C**), peptides (**2D**), carboxylic acids (**2B**, **2E**), organochlorides (**2F**), and organophosphates (**2G**). The resultant polymers could be further modified to enrich

Table 3. Tuning properties of polymer **1A** via altering polymerization conditions.

Entry	Reaction conditions		M_n [kD]	PDI	Water solubility[a] [g L^{-1}]	T_g [°C]	Potential application
	Temperature [°C]	Time [h]					
1	75	17	2.6	1.9	>100	9.7	Hydrogel
2	85	26	25.1	1.6	<1	66.2	Plastic

[a]At room temperature.

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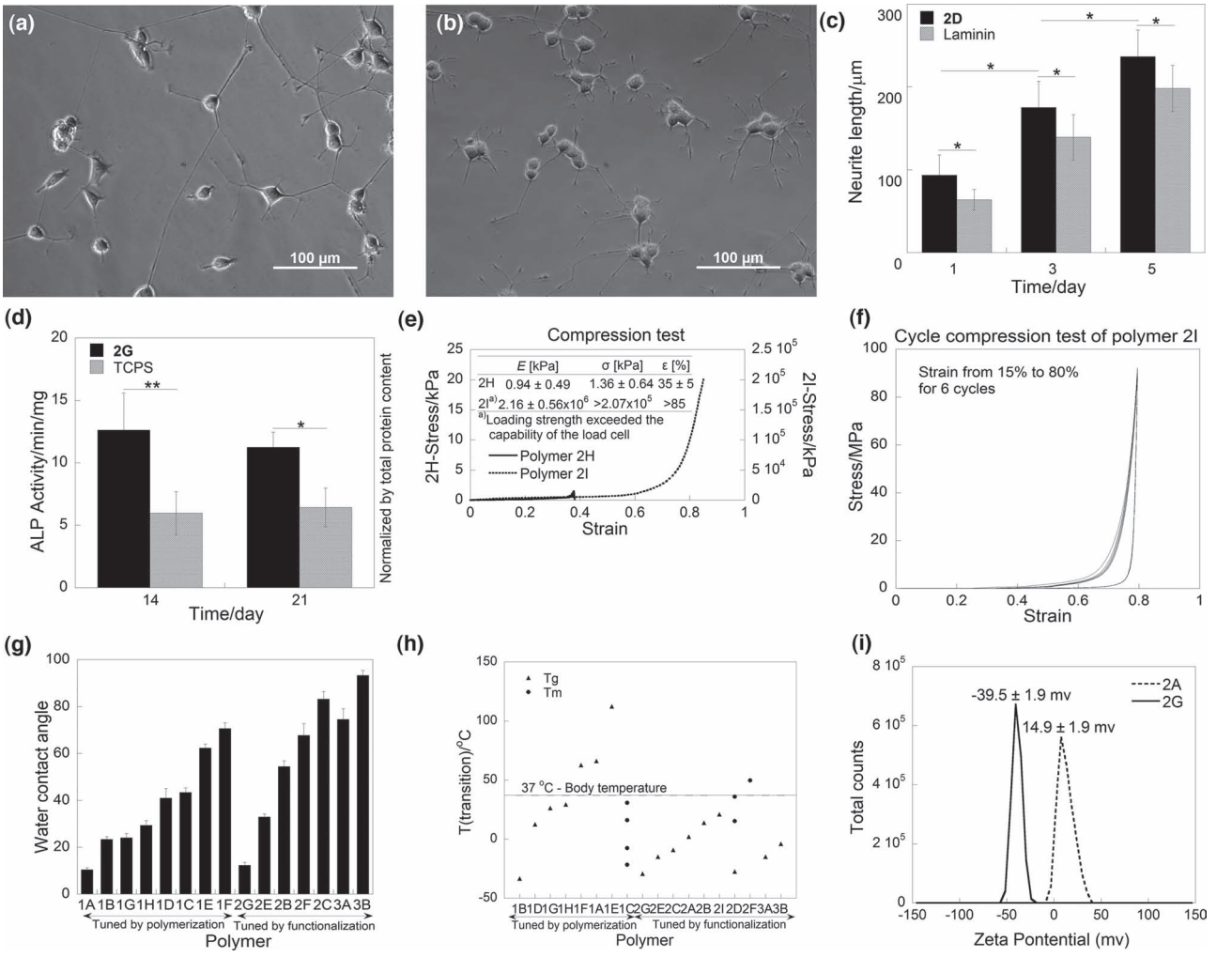

Figure 3. A wide range of physical, thermal, mechanical, and biological properties obtainable using the platform. a–d) Biofunctionalizations: differentiated PC12 cells on polymer **2D** (a) formed more extensive neurite network than those on laminin (b) at day 5 after seeding. c) The neurites of differentiated PC12 cells on polymer **2D** were longer than those on laminin and significantly grew in another day. Twenty longest neurites from 10 images on each surface per day were measured. d) The alkaline phosphatase (ALP) activity of rat osteoblasts on polymer **2G** were significantly greater than that on TCPS at day 14 and 21 after seeding. Data represent mean ± SD. Statistical significance (Student's *t* test) was marked as * ($p < 0.05$) or ** ($p < 0.01$). e,f) Mechanical properties of representative crosslinked networks. g) Control of hydrophilicity. h) Control of thermal properties. i) Characterization of the charge properties of representative polymers. Zeta potential distribution of polymer **2A** and **2G** in methanol solution.

the functionalities (**3A**). Most of the transformations had >90% conversion rate without apparent polymer degradation while preserving the PDI (Table 2). In addition to linear conjugation, these polymers can also be crosslinked by various methods including photocrosslinking of alkenyl groups (Figure 2B, polymer **2H**), condensation of the hydroxyl groups (Figure 2B, polymer **2I**), and catalyst-free [2 + 2] photoaddition of the cinnamyl groups (Figure 2C, polymer **3B**) to create polymeric networks with a wide range of structures and properties.[40–43]

2.3. Diverse Properties of the Functionalized Polymer

To control the biointerface of materials, many methods have been developed to functionalize materials with biomolecules. Most of them focus on surface modification.[44] This may perform well in non-degradable materials, but the modification will be lost upon degradation in degradable materials. Our motivation is to provide bulk biofunctionalization that will persist after the initiation of degradation. As a proof of principle, we create a neuroactive polymer **2D** (**Figure 3**A–C) and an osteoactive polymer **2G** (Figure 3D) from the same biodegradable precursor **1C** (Figure 2A). Appropriately immobilized peptides can recapitulate certain functions of the parent proteins.[45] Polymer **2D** with a laminin epitope IKVAVS promotes more vigorous neurite outgrowth of differentiated rat pheochromocytoma cells (PC12) than laminin. Laminin is the standard substrate for in vitro neuron culture, but it can not be used as a scaffolding material in vivo because it is soluble in water. Few synthetic materials have comparable neuroactivity to laminin.[45,46] The same chemistry can conjugate various peptides and proteins to the polymers to control their biointerfaces. As an alternative to

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macromolecules, small molecules can also be used to modify polymers to control biointerfaces in a simpler, more cost-effective way.[47] Modification of **1C** with phosphates creates **2G** that presents a highly phosphorylated environment resembling that of the bone. **2G** exhibits stronger in vitro osteogenetic capability than typical cell culture substrate, tissue culture treated polystyrene (TCPS, Figure 3D). These show that this method provides a simple platform for conjugating biomolecules and effectively endows the polymers with the corresponding bioactivity.

Biomaterials with a wide range of mechanical properites can be applied to a diverse range of medical applications.[43,48,49] The polymers produced here are readily crosslinkable allowing facile control of mechanical properties (Figure 3E,F), which can significantly impact cell behaviors.[50–53] The elastic moduli (E) of the polymers span over 6 orders of magnitude, from 0.94 ± 0.49 kPa (**2H**) to 2.16 ± 0.56 GPa (**2I**) (Figure 3E). The maximum compressive stress (σ) of **2I** exceeds 207 MPa, which is among the strongest polymers used for hard tissue engineering.[54] Moreover, **2I** is elastic with a maximum compression strain (ε) more than 85% and recovers from cyclic compression with 80% strain to at least 6 cycles (Figure 3F). Few biomaterials exhibit mechanical strength and elaticity comparable to those of **2I** at high strain. **2I** shows strain-dependent modulus with a biphasic profile (Figure 3E) that resembles the complex mechanical properties of some native tissues.[55] The regularly alternating structure of **2I** may account for its unique mechanical properties. We expect **2I** to be very useful in mechanically demanding applications such as tendon and ligament. To the best of our knowledge, few methods can produce materials with mechanical properties over such a broad range.[56]

In addition to bioconjugation and crosslinking, the polymers are also amenable to many other modifications (Figure 2, Table 2). Collectively the broadly applicable polymerization and robust post-modification strategies produce polymers with a wide range of structures, which can tailor the physical, chemical, mechanical, and biological properties. Other controllable properties include: 1) hydrophilicity— the polymers can be hydrophobic or hydrophilic (Figure 3G) or even water soluble (**2A**); 2) thermal properties— the polymers can be glassy and hard (**1A**, **1E**, **1F**), semi-crystalline (**2F**), or amorphous and pliable (the rest of the polymers) at body temperature (Figure 3H); 3) charge— the polymer can be neutral (**1A-1H**,**2C**, **2F**,**2H**, **2I**, **3B**), cationic (**2A**, **2D**, **3A**), anionic (**2E**, **2G**), or zwitterionic (**2B**) (Figure 3I). All these material properties can be used to control cell–material interactions.[44,47,50–52,57–61] The functional groups themselves can affect cell adhesion, spreading, and proliferation,[14] stem cell differentiation,[47] and protein absorption.[60] Furthermore, hydrophilicity,[44] charge properties,[44] physical state,[58] and stiffness[52,59,62] have significant impacts on various cell behaviors.

2.4. The Advantage of this Synthetic Method Compared to Conventional Methods

This platform technology produces functionalized polyesters difficult to synthesize by conventional methods. To exemplify the advantage of this platform, we compared it with a conventional synthesis of the representative polymer **1C**. Polycondensation of the protected glycerol and sebacic acid followed by deprotection is a standard method. However this is usually compromised by tedious protection and deprotection steps. Furthermore, selectively protection of one of the three OH groups in glycerol is complicated.[63,64] In view of these difficulties, there is no report on the synthesis of **1C** using this route. Direct polycondensation between unprotected glycerol and sebacic acid is a simple alternative to prepare **1C**. But this is compromised by premature crosslinking and low molecular weight (M_n = 1681, PDI = 1.60 in a recent report).[65] To increase the molecular weight, we performed the polycondensation of glycerol and sebacic acid under high vacuum. The resultant polymer is a highly viscous liquid with high PDI (M_n = 8.2 kD, PDI = 56.6). In contrast, **1C** is a waxy solid with good M_n, PDI, and processability (Table 1). Furthermore, the well-defined structure of **1C** enabled facile modification of hydroxyl groups (Figure 2). For example, the conjugation of **1C** with IKVAVS proceeded smoothly to form **2D** with good solubility and processability. However, the same reaction performed using the polymer made from direct condensation of glycerol and sebacic acid led to gelation suggesting crosslinking.

3. Conclusions

In summary, the acid-induced epoxide ring-opening polymerization is very practical with a wide range of starting materials, simple synthesis, and easy post-synthesis modification. The simple chemistry described here produces diverse biodegradable materials with tunable functional groups. This provides a powerful platform to tailor the properties of biomaterials for specific biomedical applications. For example, a functionalized polyester derived from **1A** has shown potential for hard tissue engineering.[66] The organohalide groups (**2F**) can undergo atom transfer radical polymerization to graft side chains with defined properties for environmentally responsive materials that are highly desirable for drug delivery and tissue engineering.[67] In addition to biomedical applications, functionalized polyesters will enrich the current collection of compostable polyesters, the most promising class of ecofriendly materials.[7,13] Similar synthetic strategy may be applied to the polymerizations between diacids with molecules containing other di-heterocycles, such as oxetane and thiiranyl groups, to produce functionalized polyesters.

4. Experimental Section

Chemical Reagents: Sebacoyl chloride (TCI, 90%), fumaryl chloride (Alfa Aesar, 95%), terephthaloyl chloride (TCI America, >99%), glycidol (Acros Organics, 96%), 2,2′-bioxirane (Sigma, 97%), and diglycidyl 1,2-cyclohexanedicarboxylate (TCI America) were distilled under reduced pressure. Triethylamine (Alfa Aesar, 99%) was dried by anhydrous NaOH (Fisher Chemical) and distilled. Sebacic acid (Alfa Aesar, 98%) was recrystallized three times from ethanol and dried under vacuum. Tetrabutylammonium hydroxide (Alfa Aesar, 55% solution), fumaric acid (Mallinckrodt, 99.5%), terephthalatic acid (Acros Organics, 98%), succinic acid (TCI America, >99%), DL-tartaric acid (TCI America, >99%), 1,2-diglycidyloxyethane (TCI America), maleic anhydride (Alfa Aesar, 99%), *tert*-butyloxycarbonyl(Boc)-glycine(Gly)-OH (Peptides International), *N*,*N*′-dicyclohexylcarbodiimide (DCC, Alfa Aesar, 99%), and 4-dimethylaminopyridine (DMAP, Avocado Research Chemicals Ltd, 99%), CF_3CO_2H (EMD Chemicals, >99.9%), Boc-Glu-O*t*Bu (Merck, ≥98%), *trans*-cinnamic acid (Alfa, Aesar, 99%), Boc-IK(Boc)VAVS(*t*Bu,

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tert-butyl)-OH (Peptide synthesis facility, University of Pittsburgh), succinic anhydride (Alfa, Aesar, 99%), $ClCH_2COCl$ (Acros Organics, 98%), pyridine (Acros Organics, 99.5%), $POCl_3$ (Alfa Aesar, 99.999%), poly(ethylene glycol) diacrylate (Aldrich, average M_n 575), 2-hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone (Irgacure 2959, Aldrich, 98%), 1,6-hexyldiisocyanate (Sigma, ≥99%), *N*-butyldimethylamine (Acros Organics, >99%), and anhydrous glycerol (J.T. Baker, >99.5%) were used without further purification. All solvents were used without further purification. Anhydrous solvents toluene, dioxane, dichloromethane, and *N*,*N*-dimethylformamide (DMF) were purchased from EMD Chemicals. Deuterated solvents for NMR analysis were purchased from Cambridge Isotope Laboratories, Inc. All other solvents were purchased from PHARMCO-AAPER.

Synthesis of Catalyst TBAS: Sebacic acid and 2 equivalent (eq) tetrabutylammonium hydroxide were mixed and stirred for 30 min in 95% ethanol at 55 °C. Almost all volatiles were removed under vacuum at 90 °C. The residual water was removed by lyophilization. The resultant TBAS was a white powder and stored in a desiccator.

Synthesis of Monomer Diglycidyl Sebacate: An anhydrous toluene solution of sebacoyl chloride was added dropwise to an anhydrous toluene solution of 2.5 eq glycidol and 5 eq triethylamine cooled in an ice/isopropanol bath (–15 °C) under a nitrogen atmosphere. After addition, the reaction mixture was stirred for another 6 h before it was filtered and concentrated. The residue was purified by flash chromatography on silica gel (hexane:ethyl acetate = 3:1) to afford diglycidylsebacate.

Synthesis of Monomer Diglycidyl Fumarate and Digycidyl Terephthalate: The compounds were synthesized using the same procedure as diglycidyl sebacate from fumaryl chloride and terephthaloyl chloride, respectively.

Typical Procedure of Polymerization: An equal molar amount of diepoxide and diacid compounds, 0.6 mol% bis(tetrabutylammonium) sebacate were mixed and dissolved in anhydrous DMF in a Schlenk flask in a glove box filled with nitrogen. The flask was sealed, transferred out of the glove box, and connected to a Schlenk line. The flask was heated and its contents were stirred under a nitrogen atmosphere. The reaction mixture was purified via typical precipitation process and dried under a vacuum (see Table 1–3 for variations of the reaction parameters).

*Synthesis of **2A***: Polymer **1C** (1 eq based on the theoretical amount of hydroxyl groups), 1.1 eq Boc-Gly-OH (Gly, glycine), 2 eq DCC, and 0.05 eq DMAP were dissolved in anhydrous dichloromethane. The mixture was stirred at room temperature under a nitrogen atmosphere for 18 h. Then it was filtered and the filtrate was concentrated. The raw product was redissolved in acetone, precipitated in ethyl ether, and washed with deionized water. The precipitate was dried under a vacuum at room temperature. The resulting solid was redissolved in trifluoroacetic acid and the solution was stirred at room temperature for 30 min. The reaction mixture was precipitated and washed with ethyl ether, and dried under a vacuum at room temperature.

*Synthesis of **2B***: Polymer **1C** (1 eq based on the theoretical amount of hydroxyl groups), 1.1 eq Boc-Glu-O*t*Bu, 1.5 eq DCC, and 0.1 eq DMAP were dissolved in anhydrous dichloromethane. The mixture was stirred at room temperature under a nitrogen atmosphere for 17 h before it was filtered. The filtrate was concentrated, washed with ethyl ether, and dried under a vacuum at room temperature. The resulting solid was redissolved in trifluoroacetic acid and the solution was stirred at room temperature for 0.5 h. The reaction mixture was precipitated and washed with ethyl ether, and dried under a vacuum at room temperature.

*Synthesis of **2C***: Polymer **1C** (1 eq based on the theoretical amount of hydroxyl groups), 1.1 eq *trans*-cinnamic acid, 1.5 eq DCC, and 0.05 eq DMAP were dissolved in anhydrous dichloromethane. The mixture was stirred at room temperature under a nitrogen atmosphere for 18.5 h. Then it was filtered and the filtrate was concentrated. The raw product was redissolved in dichloromethane, precipitated, and washed with ethyl ether. The precipitate was dried under a vacuum at room temperature.

*Synthesis of **2D***:[68] Polymer **1C** (1 eq based on the theoretical amount of hydroxyl groups), 0.3 eq Boc-IK(Boc)VAVS(*t*Bu)-OH, 0.6 eq DCC, and 0.03 eq DMAP were dissolved in anhydrous DMF. The mixture was stirred at room temperature under a nitrogen atmosphere for 68 h before it was filtered. The filtrate was concentrated, washed with ethyl ether, and dried under a vacuum at room temperature overnight. The resulting solid was redissolved in trifluoroacetic acid and the solution was stirred at room temperature for 15 min. The reaction mixture was concentrated, precipitated and washed with ethyl ether, and dried under a vacuum at room temperature.

*Synthesis of **2E***: Polymer **1C** (1 eq based on the theoretical amount of hydroxyl groups) and 2 eq succinic anhydride were dissolved in anhydrous DMF. The mixture was stirred at 100 °C under a nitrogen atmosphere for 1 h before it was concentrated. The raw product was redissolved in THF, precipitated in deionized water, and dried under a vacuum at room temperature.

*Synthesis of **2F***: An anhydrous dichloromethane solution of $ClCH_2COCl$ (3.2 eq) was added dropwise to an anhydrous dichloromethane solution of polymer **1C** (1 eq based on the theoretical amount of hydroxyl groups) and pyridine (3 eq) cooled in a dry ice/isopropanol bath (around –78 °C) under a nitrogen atmosphere. After addition, the reaction mixture was stirred in ice/isopropanol bath (–15 °C) for another 3 h before quenched by methanol. The reaction mixture was diluted by ethyl acetate and washed by deionized water for three times. Then the organic layer was dried by anhydrous Na_2SO_4, filtered, concentrated and dried under a vacuum at room temperature.

*Synthesis of **2G***: An anhydrous THF solution of $POCl_3$ (0.5 eq) was added dropwise to an anhydrous THF solution of polymer **1C** (1 eq based on the theoretical amount of hydroxyl groups) cooled in an ice/isopropanol bath (–15 °C) under a nitrogen atmosphere. The mixture was stirred for another 2.5 h before it was quenched by deionized water. The mixture was concentrated, redissolved in acetone, precipitated in ethyl ether, washed by deionized water, and dried under a vacuum at room temperature.

*Synthesis of **2H***:[69] The same mass amount of polymer **1A** and poly(ethylene glycol) diacrylate were dissolve in 1 g L^{-1} Igra2959 aqueous (5 mL g^{-1} **1A**). The solution was poured into to a plastic mold and exposed to a 365 nm ultraviolet light (4.8 mW cm^{-2}, model SB-100P, Spectroline) for 24 min.

*Synthesis of **2I***: Polymer **1F** was dissolved in THF and mixed thoroughly with 10 wt% 1,6-hexyldiisocyanate using a vortex mixer. The solution was poured into a cylinder-shape glass mold and connected to house vacuum at room temperature for 20.5 h to remove THF. Then the mixture was heated at 140 °C for 30 h to yield **2I**.

*Synthesis of **3A***: Polymer **2F** (1 eq based on the theoretical amount of chloromethyl groups) and 2 eq $CH_3COOCH_2CH_2N(CH_3)_2$ were dissolved in acetone. The mixture was stirred at room temperature for 17 h. The precipitated raw product was redissolved in methonal, precipitated in acetone, and dried under vacuum at room temperature.

*Synthesis of **3B***:[41] A thin film of **2C** was exposed to a 365 nm ultraviolet light (4.8 mW cm^{-2}, SB-100P, Spectroline) for 20 min to produce **3B** for characterizations including IR, differential scanning calorimetry, and water contact angle.

*Synthesis of **1C** by Conventional Polycondensation*: An equal molar amount of glycerol and sebacic acid was mixed at room temperature. Bubbling N_2 was passed through the mixture while it was heated to 120 °C with constant stirring. The reaction was maintained at 120 °C under N_2 for 24 h before the N_2 bubbler was removed and a vacuum line was attached. Pressure was reduced to 40 mTorr and the reaction mixture was kept at 40 mTorr and 120 °C for another 24 h. The resultant polymer was a pale and highly viscous liquid.

General Characterization: The molecular weight was determined via gel permeation chromatography (GPC) on a Viscotek GPCmax VE2001 system equipped with a Viscotek 270 dual detector (differential refractive index and right angle light scattering). For polymer **1C**, the measurement was performed on a PSS SDV 1000 Å column using THF (PHARMCO-AAPER, HPLC) as the eluent at room temperature. Polystyrene (American polymer standards PS170K) was used for calibration. For other polymers, the measurement was performed on a PSS GRAM 100 Å and 1000 Å two columns system using a dimethylacetamide (PHARMCO-AAPER, HPLC) solution of 3 g L^{-1} lithium bromide (Alfa Aesar, 99.9%), 6 mL L^{-1} acetic acid (EDM, HPLC) at 80 °C. Polystyrene (American polymer standards PS34K) was used for calibration for polymers **1A-1B**, **1D-1H**, **2C**, **2E-2G**, and **3A**. Polystyrene (Varian EasiVial PS-M, Part No. 2010-0301) was

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used for conventional calibration for polymer **2A**, **2B**, and **2D**. ^{1}H and ^{31}P nuclear magnetic resonance (NMR) spectra were recorded on Varian Mercury 400 NMR, Bruker 400 NMR, or Bruker Avance 600 NMR (see the note with the spectra). Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were recorded on Thermo Nicolet IR iS 10 spectrometer unless noted otherwise. Differential scanning calorimetry of the polymers was performed on a TA DSC Q200 at a heating rate of 10 °C min^{-1} under a nitrogen atmosphere. Water contact angle was recorded on AST PRODUCTS INC. VCA2000 instrument. Inductively coupled plasma atomic emission spectra were recorded on a Thermo Fisher Scientific iCAP 6500 duo ICP spectrometer. UV spectra were recorded on a Bioteck SynergyMX plate reader. Zeta potential was recorded on a Malvern Zetasizer Nano-ZS90.

Mechanical Test: Hydrogel **2H** was synthesized as described previously and then punched to proper disk-shaped samples; typical sample sizes were 5.4 mm in diameter and 4.2 mm in height. The compression test was conducted in a water bath at room temperature on an MTS insight mechanical analyzer equipped with a 5 Newton load cell. Test speed was kept at 1 mm min^{-1}. The sample was compressed to failure. Elastic modulus was determined from the initial part of the stress–strain curve. Three samples were tested and averaged. Cylindrical samples of polymer **2I** were synthesized as described previously and then cut to proper length; typical sample sizes were 3.5 mm in diameter and 7.0 mm in length. The compression test was conducted on an Instron 5564 mechanical analyzer equipped with a 2000 Newton load cell according to ASTM standard D695-02a. Test speed was kept at 0.5 mm min^{-1}. In the simple compression strength test, the sample was compressed to reach the maximum capability of the load cell (for safety reason, it was set on 1800 Newton). The elastic modulus was determined from the end part of the stress–strain curve. Three samples were tested and averaged. In the cyclic tensile strength test, the sample was compressed to 80% then allowed to recover to 15% before immediately being compressed to 80% six times.

*In Vitro Cell–Material Interaction of Polymer **2D***: Polymer **2D** was coated on tissue culture treated polystyrene (TCPS) surfaces. Methanol solution of **2D** (1 g L^{-1}) was filtered through a 0.2 µm filter and added to a 24-well TCPS plate (80 µL per well). The plate was dried under vacuum overnight after evaporation of the solvent in air, sterilized by UV light for 30 min, then washed with phosphate buffered saline three times and culture medium (Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% heat-inactivated horse serum, and 5% fetal bovine serum (FBS)) once with gentle shaking (1 mL per well). TCPS coated with 200 µL of laminin (BD Biosciences, #354232) in molecular grade water (50 mg L^{-1}) by gently shaking overnight was used as a control. PC12 cells were maintained in a humid, 5% CO_2 incubator at 37 °C. The cells were primed for 24 h in differentiation medium (DMEM, 1% heat-inactivated horse serum, 0.5% FBS, 50 ng mL^{-1} nerve growth factor) before seeding at a density of 1×10^4 per cm^2. The cells were maintained in an incubator with medium exchanged every 2 days. On day 1, 3, and 5, the phase contrast images were taken using an inverted microscope Eclipse Ti (Nikon, Melville, NY) equipped with a RETIGA-SRV digital camera (QImaging, BC, Canada). The longest 20 neurites from 10 images on each surface per day were measured using NIH ImageJ version 1.42. Neurite length was defined as the distance from the tip of the neurite to the junction between the cell body and neurite base. In the case of branched neurites, the length of the longest branch was used.

*In Vitro Cell–Material Interaction of Polymer **2G***: Polymer **2G** was coated on TCPS surfaces. Methanol solution of **2G** (1 g L^{-1}) was filtered through a 0.2 µm filter and added to a 24-well TCPS plate (80 µL per well). The plate was dried under vacuum overnight after evaporation of the solvent in air, sterilized by UV light for 30 min, then washed with phosphate buffered saline three times and culture medium (DMEM with 10% FBS) once with gentle shaking (1 mL per well). Untreated TCPS was used as control. Osteoblasts (passage 4) isolated by sequential trypsin-collagenase digestion of calvaria of neonatal (2–3 days old) Sprague-Dawley rats was seeded at a density of 1×10^4 per cm^2 and maintained in a humid, 5% CO_2 incubator at 37 °C.[70] The medium was changed every 2 days. Alkaline phosphatase activity was measured using a commercial kit (Sigma, #P7998) and normalized by total protein concentration (Thermo Scientific, Pierce 660 nm protein assay kit) and minutes after 14 and 21 days culture. At least four replicas were performed. All spectroscopic absorption was determined by a SynergyMX plate reader (Biotek, Winooski, VT).

Statistical Analysis: For cell culture experiments, two-tailed Student's *t* test was used to compare the polymer and the control. A p value of <0.05 was considered statistically significant. All data are reported as mean ± standard deviation.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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