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Elastomeric polyamide biomaterials with stereochemically tuneable mechanical properties and shape memory

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Biocompatible polymers are widely used in tissue engineering and biomedical device applications. However, few biomaterials are suitable for use as long-term implants and these examples usually possess limited property scope, can be difficult to process, and are non-responsive to external stimuli. Here, we report a class of easily processable polyamides with stereocontrolled mechanical properties and high-fidelity shape memory behaviour. We synthesise these materials using the efficient nucleophilic thiol-yne reaction between a dipropiolamide and dithiol to yield an $\alpha,\beta$ – unsaturated carbonyl moiety along the polymer backbone. By rationally exploiting reaction conditions, the alkene stereochemistry is modulated between 35–82% cis content and the stereochemistry dictates the bulk material properties such as tensile strength, modulus, and glass transition. Further access to materials possessing a broader range of thermal and mechanical properties is accomplished by polymerising a variety of commercially available dithiols with the dipropiolamide monomer.
The ability to rationally modulate the thermomechanical properties of polymeric materials by design is a fundamental aim of materials science. It is well known that stereochemistry of polymers dictates their bulk properties, but the importance of stereocontrol in polymer synthesis is often overlooked. For example, the naturally occurring isomers of polyisoprene—natural rubber and gutta-percha—display stereochemically dependent thermomechanical properties where the cis orientation of the alkene moiety disrupts chain packing and leads to a much softer, more amorphous material. Such striking structure–property relationships are often found in stereochemically precise biopolymers, e.g., collagen or elastin, but there remain significant limitations in synthetically mimicking these complex biological materials. Achieving control over stereochemical assembly of monomers into synthetic polymers, particularly backbone stereochemistry, could afford a simple platform from which to access a diverse range of materials properties. This is of particular importance when considering the unique mechanical needs of biomaterials operating in diverse physiological environments.

Synthetic polymers have been used in medical devices for more than five decades, and key recent advances have largely focused on the development of biodegradable (or resorbable) materials for tissue engineering. As such, the continued innovation of long-lasting non-resorbable polymers in joint and/or bone therapies, for example, are lagging behind and suffer from notable limitations such as wear, difficult processing, sterilisation or high cost. Nevertheless, polyamides have been a biomaterial of choice for decades and they have been extensively developed for applications ranging from use as sutures or membranes to vascular grafts and they have been extensively developed for applications ranging from use as sutures or membranes to vascular grafts.

We set out to create a tough, resilient biomaterial with stereochemically dependent properties by combining a polyamide backbone with unsaturated alkene moieties. Synthetic heteroatom-containing polymers featuring stereocontrolled unsaturated moieties along the main chain are not very abundant. Nonetheless, polyesters or poly(ester-amide)s, prepared with pre-defined stereochromatic units, such as fumaric acid, have garnered attention as biomaterials. However, maleate-based materials have been notoriously hard to prepare and functionalise, which has ultimately limited their performance in other applications. An ideal durable biomaterial platform would incorporate the thermomechanical and biological performance of polyamides while displaying enhanced processability and advanced functionality, such as shape memory, for minimally invasive device designs.

We describe here the mild nucleophilic thiol-yne addition of dithiols to a dipropiolamide monomer to produce stereocontrolled unsaturated polyamides possessing robust thermomechanical and optical properties. The presence of both amide and unsaturated moieties along the backbone imbue the materials with unique properties, namely shape-memory behaviour and stereochemically dependent thermomechanical properties.

Results

Synthesis of stereocontrolled polyamides. Recently, the nucleophilic Michael addition reaction between nucleophiles and activated alkenes (amino-yne, phenol-yne and thiol-yne) has attracted considerable attention as an efficient path to step-growth polyesters. There has been some progress in controlling the stereochemistry of the resultant alkene in the backbone, but many “yne-type” polymers are not synthesised in a stereocontrolled manner, despite the well-established impact of double-bond stereochemistry on bulk material properties (e.g., glass transition and stiffness). Initially, we screened reaction conditions that were used for the analogous stereocontrolled reaction between thiols and propiolate esters. The combination of a dipropiolamide monomer (C3A) (Supplementary Figs. 1 and 2), 1,6-hexanediol (C6T) and 1 mol% 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dimethyl sulfoxide (DMSO) afforded a fibrous solid after isolation from the reaction mixture (Fig. 1a). After drying, the solid was analysed using 1H NMR spectroscopy and the product showed characteristic vinyl proton resonances (73% cis) indicative of a thiol-yne addition (Fig. 1b; Supplementary Figs. 3 and 4). Finally, size-exclusion chromatography (SEC) confirmed high molecular mass polymers (Fig. 1c; Supplementary Fig. 20).

Next, the stereochemistry of the vinyl thioether moiety in the polymer backbone was modified by changing either the polarity of the reaction medium and/or the base catalyst. Although DMSO was critical for polymer solubility, the overall polarity of the reaction mixture could be modulated to be less polar (dilution with chloroform) or more polar (dilution with methanol). Qualitatively, the reaction between the propiolamide and thiol is sluggish compared with the propiolate analogue, thus limiting the choice of suitable base catalysts. A variety of organic bases were screened, including triethylamine (NET3), only yielding oligomeric species. However, by employing 1,4-diazabicyclo[2.2.2]octane (DABCO) at higher loadings (10 mol%), we could isolate high molecular mass polymers (Mw ≥ 100 kDa) and we chose DABCO as the “weak” base (pKa (H–DABCO) = 8.8 versus, pKa (H–DBU) = ca. 12). Our initial reactions (using DBU and DMSO) afforded polymers with moderately high cis content (ca. 70%) (Table 1, entry P2). The cis content could be increased by adding methanol to the DMSO/DBU reaction mixture (Table 1, entry P1). To decrease the cis content in the resultant polymers, progressively greater amounts of chloroform were added to the DMSO reaction mixture, and DBU was
substituted with DABCO (Table 1, entries P3–4; Supplementary Figs. 7–10).

Additional propiolamide monomers with longer methylene spacers (such as C4A, C5A and C6A) were active in the step-growth polyaddition reaction using our optimised conditions, but the resultant material would precipitate from the reaction mixture as an intractable powder. Since we could not adequately characterise these polyamides because of their low processability, we excluded them from this study.

Thermal and mechanical properties. The thermal properties of the materials were initially probed using thermogravimetric analysis (TGA) and the degradation temperatures ($T_d$) were ≥300 °C, indicating excellent thermal stability (Supplementary Fig. S21). Differential scanning calorimetry (DSC) of the polymers showed a broad glass transition ($T_g$) and no discernible melt transition ($T_m$) (Fig. 2a; Supplementary Fig. 22). Nevertheless, the $T_g$ displayed a positive correlation with %cis content as indicated by Δ$T_g$ = 14 °C between P4 (35% cis) and P1 (82% cis) (Fig. 2b; Supplementary Fig. 23). The thermal behaviour suggested that the materials were largely amorphous and surface imaging of P1 using atomic force microscopy (AFM) also revealed a non-crystalline morphology (Supplementary Fig. 39). Prolonged annealing below and/or above the respective glass transition temperature also did not induce any crystallisation in P1 (Supplementary Fig. 26). Repeated cycling of the polymers during thermal analysis also led to a decrease in modulus, which may

| Table 1 Characterisation of material properties for polymers obtained using different polymerisation conditions for C3A and C6T using 1 mol% base at [C3A] = 1 M. |
|---|
| Entry | Solvent | Base | %cis | $M_w$ (kg mol$^{-1}$) | $E$ (MPa) | ε-break (%) | UTS (MPa) | $T_g$ (°C) |
| P1 | DMSO/MeOH (2:1) | DBU | 82 | 104.6 | 1278.4 ± 42.1 | 109 ± 28 | 70.4 ± 2.6 | 98 |
| P2 | DMSO | DBU | 73 | 131.4 | 1219.3 ± 48.0 | 158 ± 55 | 67.9 ± 4.2 | 94 |
| P3 | DMSO/CHCl$_3$ (1:1) | DBU | 46 | 111.8 | 1111.7 ± 19.6 | 158 ± 45 | 60.9 ± 3.9 | 83 |
| P4 | DMSO/CHCl$_3$ (1:2) | DABCO | 35 | 112.5 | 1052.5 ± 74.2 | 138 ± 87 | 65.5 ± 8.3 | 84 |
| Nylon 6 | Commercial sample | | | | | | | |
| Nylon 6,6 | Commercial sample | | | | | | | |

%cis content determined by $^1$H NMR spectroscopic analysis. $^aM_w$ determined by SEC (DMF, 0.5% w/w NH$_4$BF$_4$) analysis against poly(methyl methacrylate) (PMMA) standards. Mechanical data ($E, \varepsilon$-break and UTS) calculated from $n \geq 3$ samples. $\pm$ represents ±1 s.d. Nylon 6,6 was averaged from $n = 2$ samples. Nylon 6 and Nylon 6,6 were commercial samples and are not soluble in the reported SEC solvent. $^c$Reported from the DSC thermograms of 2nd heating cycle. $^d$In total, 10 mol% (relative to monomer) was used.
have been due to undesirable cross-linking reactions or possibly isomerization of the alkene moiety. However, according to \textsuperscript{1}H NMR spectroscopic analysis, negligible isomerization of the alkene (73 versus 71\% cis) occurred after protracted heating of a sample (ca. 12 h, 150 °C, N\textsubscript{2} atmosphere) (Supplementary Fig. 19).

It became clear that the properties of the unsaturated polyamides were very different from those of common saturated polyamide analogues, such as Nylons, and it was perhaps most obvious when comparing their physical appearance (Fig. 2c). Variable temperature tensile testing of the high \textsuperscript{1}H cis polymer showed that as the polymer approached its glass transition temperature it softened significantly, with a concomitant improvement in ductility (Fig. 2d). To our surprise, when testing the material above the glass transition temperature we observed elastomeric behaviour; this occurrence contrasts distinctly with the thermoplastic nature of Nylons under similar conditions (Fig. 2e). However, the mechanical profiles of both classes of polyamides were comparable at ambient temperature (Supplementary Fig. 33). These results suggest that this class of stereocontrolled, unsaturated polyamides can match the mechanical strength of Nylons, but with the added benefit of temperature-tuneable mechanical properties. As a control experiment, we synthesised a Nylon 3,14 derivative in order to model the composition of the C\textsubscript{3}A-C\textsubscript{6}T polymers. As expected, this polymer was similar to the commercial Nylons (and different to our amorphous polyamide) as evidenced by its semi-crystalline nature (Supplementary Fig. 27).

Additional investigation of the mechanical properties for polymers with different stereochemistry was then conducted. Overall, the polyamides possessed high moduli with moderate ductility. Specifically, the mechanical properties are comparable with Nylon 6,6, which is a useful biomaterial for numerous applications. The Young’s modulus (E) of the materials ranged from 1052 ± 74 MPa (35\% cis) to 1278 ± 42 MPa (82\% cis), and stiffness increased accordingly with cis content; this trend was also very similar for glass transition temperature (Fig. 2b; Supplementary Fig. 31). It was found that there is a statistical difference (P < 0.05) between the elastic moduli of materials with very high (≥73\%) cis content and those with low (≤46\%) cis content. However, the elastic moduli differences between the 35 and 46\% cis materials was found to be statistically insignificant. An inverse relationship is generally true for plasticity where the lowest strain at break (ε\textsubscript{break}) was observed for P1 (ε\textsubscript{break} = 109 ± 28\%). The strain at break for P4 (ε\textsubscript{break} = 138 ± 87\%) was not drastically different from P1 and was found to be statistically insignificant. However, it should be noted that the P4 trials were less reproducible with one sample exceeding 200\% elongation. The lack of reproducibility is also apparent when examining the relatively high standard deviations for the E and σ\textsubscript{stress} (Table 1, entry P4). However, another sample with similarly high trans content (37\% cis) was much more reproducible and had a significantly higher strain at break albeit the molecular mass of the sample was considerably greater (Supplementary Fig. 31).

Shape memory properties. Many implants would benefit from minimally invasive attributes to reduce surgical trauma and therefore time to healing. Shape memory behaviour could potentially provide a minimally invasive route for implantation by reducing the material footprint during surgery and it may also increase the implant’s resilience to certain deformations or damage. Although shape memory alloys have been developed for hard tissue applications, they are beset by long-term biocompatibility issues and most shape memory polymers for
biomedical use are more similar to soft biological tissues (e.g., hydrogels)\textsuperscript{67,68}. The introduction of a more tuneable and dynamic non-resorbable biomaterial possessing excellent biocompatibility and robust mechanical properties could be extremely useful to provide a fine degree of control over the material’s behaviour.

We discovered that all formulations displayed shape memory behaviour (Supplementary Tables 1 and 2), a rare phenomenon in polyamides that has previously only been observed in thermostet materials\textsuperscript{24,69}. An important note to make is that these thermoplastics display good initial shape recovery, on par with cross-linked materials containing permanent net-points which help promote their original shape structures. In our system, it is likely that these features are a result of robust chain entanglements (due to high-molecular-weight) and entropic free-energy contributions combined with a high degree of hydrogen bonding among the amide moieties. We attempted to more precisely identify the origin of the shape memory behaviour by examining the surface morphology below and above the $T_g$ of P1 using AFM; however, no significant micro- or nano-scale morphological changes were visible (Supplementary Fig. 39). We are still probing the molecular emergence of the shape memory.

Regardless of stereochemistry, full strain recovery and strain fixation were achieved (Fig. 3; Supplementary Table 1). Following the trends revealed by thermomechanical analysis, high cis polymers displayed reduced strains (in line with the mechanical behaviour of the system). However, the high cis polymers were also more likely to undergo shape recovery when approaching the $T_g$ (at the increase of the dampening ratio as determined by tan $\delta$), while the low cis polymers required prolonged isothermal equilibrium at 120 $^\circ$C (well above the $T_g$) to achieve full strain recovery (Fig. 3b). The slower recovery of the low cis samples may be a consequence of the better polymer chain packing that is afforded by relative abundance of hydrogen bonding around individual chains. On the other hand, high cis polymers may have a decreased relative concentration of hydrogen bonding because of a more open molecular structure, and therefore reduced interactions with surrounding carbonyl moieties.

We also investigated the durability by performing cyclic shape memory experiments, including examining differences that could result from stereochemistry as well as choice of thiol comonomer (Supplementary Figs. 29 and 30, Supplementary Table 3). Regardless of composition, shape memory performance decreased after cycling (especially after ten cycles). This diminished cyclic repeatability in the shape memory behaviour is not unexpected for thermoplastic shape memory materials and may also be attributable to fatigue in the macroscopic film. Importantly, potential medical applications that make use of shape memory behaviour to produce minimally invasive devices do not require a material to behave as an actuator. Rather, a single shape-recovery response is necessary for minimally invasive surgeries. The performance of the polyamides displayed here meet these criteria and could be suitable in such applications.

**Biocompatibility studies.** Hydrolytic stability and water uptake behaviour were assessed for a high trans sample (33% cis, $M_w = 109$ kDa) and a high cis sample (86% cis, $M_w = 123$ kDa). The polymers were processed into disks via heated compression moulding, and the accelerated degradation profiles were assessed in triplicate in PBS, 1 M KOH and 5 M KOH solutions at 37 $^\circ$C (Supplementary Fig. 36). For both polymers, minimal degradation and slight swelling were observed, irrespective of the medium, which indicated that this polymer class has robust hydrolytic stability. However, the swelling was more significant in the high cis samples (135 ± 5.7%, 1 M KOH) compared with the high trans samples (107 ± 4.4%, 1 M KOH). This trend is somewhat surprising since both materials are amorphous and have similar thermal profiles, but it is consistent with the hypothesis that stereochromically dependent shape memory recovery behaviour results from the closeness of packing of the polymer chains in the bulk material. Regardless of the medium, the high trans materials

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**Fig. 3** Shape memory behaviour. a Visual demonstration of shape memory for C$_3$A-C$_6$T 82% by heating to 120 $^\circ$C. Note: Sample edges were darkened with ink to aid in visualising movement. b DMA analysis of shape memory behaviour for C$_3$A-C$_6$T (high cis and low cis).
Initially swelled to a maximum water uptake after 10 days followed by a slow decrease in mass (relative to maximum), but the high cis materials continued to swell throughout the duration of the study. These results indicate that stereochemistry also affects water uptake behaviour, and subsequently the overall hydrolytic stability, which could also be leveraged in the future design of biomaterial devices and implants.

In order to investigate the potential for use in biomaterial applications, a proliferation assay was used as an initial method to determine cellular responses to all polyamides (C3A-C6T cis/trans, or P1 and P4, and high cis polymers of other composition). Mouse osteoblasts (MC3T3-E1) were cultured in cell culture medium containing 10% foetal bovine serum on thin discs of the polyamide or on the control polymer, poly(L-lactide) (PLLA). Cell proliferation was measured with a PrestoBlue metabolic assay, after 1, 3 and 7 days of incubation. This cell line is generally considered as a suitable cell model for studying material cytocompatibility. After 7 days, the number of cells on each sample had increased dramatically, indicating good cytocompatibility (Fig. 4a). Statistical analysis (P < 0.05) revealed a superior cytocompatibility of C3A-C6T cis and C3A-C6T compared with the PLLA control, while C3A-DEGT was found to support cell proliferation less than PLLA.

The in vivo biocompatibility of high cis C3A-C6T (P1) was subsequently examined over 8 weeks in murine subcutaneous implantation studies. Hematoxylin and eosin staining (H&E staining) was used to detect fibrous capsule granuloma formation and inflammatory cell presence, based upon ISO 10993-6 standards as assessor metrics, where individual slides were assessed for cell presence and numbers and assigned an inflammatory score at the tissue-material interfacial region (Table 2). Comparisons to PLLA controls indicated that the selected polyamide was both biocompatible as well as biostable. PLLA is considered a gold standard for implantable synthetic polymers and does not degrade over the time frame of the in vivo studies (8 weeks), hence we selected it as a suitable control for this experiment. Moreover, the biocompatibility of nylon has long been established in a variety of different animal models. Capsule formation in both species was found to be <200 µm and uncalcified, which indicated that no severe inflammatory response occurred as a consequence of the presence of the material and is within the range of an accepted response for an implantable material (Fig. 4b).

The absence of necrosis was a further indication of the biocompatibility of this polymer system, and the reduced macrophage presence outside the tissue capsule indicated low particulate formation and inflammation related to material degradation. The presence of macrophages at the implant-tissue interface was expected and provided evidence of implant site healing. Similar macrophage loads at both the control and polyamide sites supported our claims of being a weakly immunee-activating biomaterial, as PLLA is a well-known biomaterial used in a wide variety of implantable materials/devices across multiple species. Both materials displayed inflammatory cell levels and species that were consistent with low level inflammation, indicating good biocompatibility of the materials.

We also investigated the in vivo stability of the materials by comparing post-implanted samples (at 4-week and 8-week time points) against samples that had not been implanted. IR spectroscopic analysis of the samples indicated that the material composition was remarkably consistent before/after implantation as evidenced by the absence of any changes to their absorption spectra (Supplementary Fig. 37). However, we noted changes in the 1H NMR spectra among the samples, particularly for the 8-week sample (Supplementary Fig. 38). We observed new low-field proton resonances (δ = 1.0 – 4.5), but these may be explained by histological processing techniques (i.e., incomplete rinsing or cleaning of the sample). There were also minor variations in the vinylic resonance region (δ = 7.0 – 7.5), suggesting some interaction or reactivity of the polymer in the biological media. Nevertheless, the IR spectra and physical appearance remained nearly identical among the samples. Finally, we observed reasonable maintenance of mechanical properties when samples were immersed in aqueous media as evidenced by immersion DMA experiments and tensile testing of “wet” samples (Supplementary Figs. 34 and 35). Together, these data suggest the materials are quite stable in application settings.

Modulation of material properties by varying thiol comonomer. After examining the C3A-C6T polymers, other thiol comonomers were polymerised with C3A to examine the effect that the thiol comonomer had on thermomechanical properties of the resultant polymers (Table 3; Supplementary Figs. 11–20, Supplementary Notes 1–4). In order to control for the effects of stereochemistry, all polymers were targeted for high cis content (ca. 80%) using the conditions for the synthesis of P1 (Table 1, entry P1). Differential scanning calorimetry (DSC) of the high cis polymers also revealed the absence of a θ transition similar to P1-4 (Supplementary Fig. 24). Nevertheless, the T_g displayed a positive correlation with % cis content. Unsurprisingly, as the number of carbon atoms increased in the thiol moiety (C3, C6, C9 and C13)
the $T_g$ decreased (Fig. 5b; Supplementary Fig. 25). The mechanical properties (such as $E$ and $\varepsilon_{break}$) followed a similar trend and these differences among samples were found to be statistically significant ($P < 0.05$) (Fig. 5a; Supplementary Fig. 32). However, as the linker length increased the ductility of the materials also greatly improved ($C_3A-C_10T$, $\varepsilon_{break} = 24 \pm 3\%$ versus $C_3A-C_8T$, $\varepsilon_{break} = 313 \pm 19\%$) and these differences were statistically significant as well. Importantly, no significant differences in shape-memory behaviour, either the strain fixation or the recovery stress, were observed among the compositions (Supplementary Table 2).

The most interesting mechanical properties were displayed by the $C_3A-C_{DEG}T$ polymer, which incorporated ethers in the repeat unit. The introduction of the diethylene glycol moieties into the polymer backbone resulted in a material with the lowest $T_g$ and we predicted this would lead to softer, yet more ductile material (Fig. 5b). In fact, $C_3A-C_{DEG}T$ was more ductile ($\varepsilon_{break} = 313 \pm 19\%$) than other materials and was found to be statistically different ($P < 0.05$) from all compositions except $C_3A-C_10T$. But remarkably, it also possessed the greatest modulus ($E = 1623 \pm 77$ MPa) and yield stress (78.1 $\pm$ 2.4 MPa) for the entire polymer series (Supplementary Table 4), although these values are not statistically different from the $C_3T$ or $C_8T$ polymers. A similar enhancement of mechanical properties has previously been observed in poly(ether-thioureas) as compared to poly(alkyl-thioureas)75. The authors proposed that the extra H-bond acceptors (etheral oxygen atoms) increased the H-bonding interactions between the polymer chains without inducing crystallisation. Our results further suggest that incorporating etheral oxygen atoms into polymers displaying significant hydrogen bonding (e.g., polyamides or polythioureas) may present a path to processable materials with high toughness. Furthermore, by decreasing the $T_g$, the transition temperature of the shape memory was closer to a biologically compatible temperature (Supplementary Fig. 28 and Supplementary Table 2).

The thermomechanical properties were tuned either by modulating the stereochemistry of the alkene moiety in the backbone or changing the thiol comonomer. Materials with high cis content were stiffer and less ductile than high trans polymers, but this was not correlated with crystallinity since all polymers appeared to be amorphous. In vitro cytocompatibility and in vivo assessments indicated that these materials possess excellent stability and bio-compatibility, which suggests that they could serve as adaptive, non-resorbable biomaterials. Nylons have traditionally been some of the most versatile biomaterials due to material property tuning which may be achieved solely through compositional adjustment; however, the system presented offers multiple possibilities for precise property modulation. Our polyamides have comparable mechanical performance to nylons but are strikingly more adaptive and easier to process. The unique combination of biostability and modifiable thermomechanical properties, in addition to the aging behaviours revealed during shape-memory testing, open avenues to durable biomedical devices such as arterial grafts, heart valves and sewing cuffs. In these applications, the tuneable mechanical properties of the materials presented here, along with their stability, would allow for consistent, life-long performance after implantation.

**Discussion**

In conclusion, the nucleophilic thiol-yne addition was exploited to synthesise a family of stereochemically controlled polyamides.
ca. >5 °C. The precipitate was collected using vacuum filtration and washed with cold water (5 x 25 mL) to afford a light-yellow solid. After drying on the benchtop at 22 °C for 24 h to remove water, the compound was purified by recrystallisation (cooling to –20 °C for ca. 16 h after heating) from a mixture of chloroform/methanol (5/1) to afford the title compound as a pale-yellow solid.

The reaction mixture was placed in a water bath (ca. 15 °C) and 1,9-diazenacyclo[5.4.0]undec-7-ene (DBU) (32.9 µL, 0.22 mmol, 0.01 equiv) was injected in one portion. The solution was diluted with methanol (200 mL) and stirred for 30 min. Then, the solution was diluted with DMSO (500 mL) for 75.54, 36.66, 73.06, 29.73, 28.27. = m signals due to rotamers. HRMS (ESI-TOF) (m/z): [M + H]+ calculated for C₉H₁₀N₂NaO₂, 201.0633; found, 201.0634.

**Representative polymerisation of C₄A-C₃T polymers.** A 100-mL round bottom flask was charged with C₄A (4.00 g, 22.4 mmol, 1.00 equiv) and a separate 20-mL scintillation vial was charged with C₃T (3.31 g, 22.1 mmol, 1.000 equiv). The thiol content polymers were determined using a TGA/DSC 1-Thermogrammetric Analyzer (Mettler Toledo). Thermograms were recorded under an N₂ atmosphere at a heating rate of 10 °C min⁻¹, from 50 to 500 °C, with an average sample weight of ca. 10 mg. Aluminium pans were used for all samples. Decomposition temperatures were reported as the 5% weight loss temperature (T₅₉₅).

**Thermogravimetric analysis (TGA).** TGA thermograms were obtained using a TGA/DSC 1-Thermogrammetric Analyzer (Mettler Toledo). Thermograms were recorded under an N₂ atmosphere at a heating rate of 10 °C min⁻¹, from 50 to 500 °C, with an average sample weight of ca. 10 mg. Aluminium pans were used for all samples. Decomposition temperatures were reported as the 5% weight loss temperature (T₅₉₅).

**Mechanical property measurements (film preparation and uniaxial tensile testing).** Thin films of each polymer were fabricated using a vacuum compression machine (TMP Technical Machine Products Corp.). The machine was preheated to 170 °C. Then polymer was added into the 50 x 50 x 1.00-mm mould, and put into the compression machine with vacuum on. After 15 min of melting, the system was degassed three times. Next, 10 lbs*1000, 15 lbs*1000, 20 lbs*1000, 25 lbs*1000 of pressure were applied consecutively for 2 min each. After that, the mould was cooled down with 1000 psi of pressure to prevent wrinkling of the film’s surface. The films were visually inspected to ensure that no bubbles were present in the films. Dumbbell-shaped samples were cut using a custom ASTM D6-638 Type V. The dimensions of the neck of the specimens were 7.11 mm in length, 1.70 mm in width and 1.00 mm in thickness.

**Differential scanning calorimetry (DSC).** The thermal characteristics of the polymer thin films were determined using differential scanning calorimetry (STARe system DSC3, Mettler Toledo) from 0 to 180 °C at a heating rate of 10 °C min⁻¹ for three heating/cooling cycles unless otherwise specified. The glass transition temperature (T_g) was determined from the inflection point in the second heating cycle.
Dynamic mechanical analysis (DMA). Dynamic mechanical thermal analysis (DMA) data were obtained using a Mettler Toledo DMA 1-star system and analysed using the software package STARTECH V.190a (b = 1997). Thermal sweeps were conducted using bar-shaped films (11.00 mm in length × 6.00 mm in width x 1.00 mm in thickness) cooled to −80 °C and held isothermally for ca. 5 minutes. Storage and loss moduli, as well as the loss factor (ratio of tan δ), were plotted as a function of temperature. The sample was then heated at 10 °C min−1 up to 120 °C, where the samples were held isothermally for 20 min to allow for total shape recovery to take place. The temperature at which strain recovery began was labelled as the recovery temperature, and the final recovered strain was the recoverable strain for the materials. Sample behaviour was averaged for n = 3 films.

Cyclic shape memory. Performance evaluation was conducted using bar-shaped films (0.5 mm x 6 mm x 20 mm). The sample was first heated to 20 °C above the Tg of the material, where samples were held until equilibrated. At this point, the proximal film end was fixed, and its distal end was bent, with the film uniformly bent around a central shaft until the distal end was parallel to the proximal. The sample was then heated at 10 °C min−1 to 120 °C, where the samples were held isothermally for 20 min to allow for total shape recovery to take place. The temperature at which strain recovery began was labelled as the recovery temperature, and the final recovered strain was the recoverable strain for the materials. Sample behaviour was averaged for n = 3 films.

Atomic force microscopy (AFM). AFM was performed on a JPK Nanowizard 4 system fitted with a heater-cooler module to control sample temperature (24–90 °C) during imaging. Images were acquired in the supplied acoustic enclosure and with vibration isolation, using a Nanosensor PPP-NCHAuD tip with a spring constant of 10 N m⁻¹. For data acquisition and handling Nanowizard Control and Data Processing Software V.6.1.117 in Q mode with a set point of 100 nN and pixel time of 8 ms was used. In this mode, a force/distance curve is collected for each pixel in the acquired image. Adhesion was calculated by first subtracting the baseline from each force curve and then identifying the lowest point of the retraction force curve. Slope, a proxy for the Young modulus of the material, where samples were held until equilibrated. At this point, the mechanical constraint was removed, and strain fixation was measured optically over a 5-min period. The sample was then heated to 20 °C above the Tg of the material, where samples were held until equilibrated with the shape recovery measured optically at 5 s intervals. Final recovered strain was determined as a function of recovered deformation of the distal end compared with the fixed proximal end. This was repeated for 60 cycles for each film, with n = 3 films per examined species.

Hydrolytic degradation studies. Accelerated degradation studies were conducted under conditions previously reported by Lam et al. All polymers (n = 3 for each composition in each solution, 18 total samples) were prepared as “degradation disks” (ca. 0.1 g) using heated compression moulding and subjected to aqueous environments of various pH (PBS, 1 M NaCl, NaOH, and 5 M NaOH). The disks were placed in individual vials containing 20 mL of the corresponding solution and incubated at 37 °C with constant agitation at 60 rpm. Before analysis, the surface of each disk was dried in order to remove excess water before the weight was periodically measured using an analytical balance.

In vitro cell studies. Polyamides were moulded into thin discs (ca. 0.3-mm thickness) with flat surfaces using compression moulding at 170 °C between two glass slides. PLLA was spin-coated onto a glass slide from a chloroform solution. MCT33-E1 cells (ATCC, CRL-2593) were seeded at a density of 4000 cells cm⁻² on top of the polymer films and cultured at 37 °C and 5% CO₂ in a-MEM enriched with 10% FBS and 1% pen/strep. Viability was detected after 24 h, 72 h and 7 days of incubation using PrestoBlue proliferation assay and following manufacturer instructions. Fluorescence (λex = 530 nm, λem = 590 nm) was measured using a BioTek plate reader. Statistical analysis was performed using an ordinary two-way ANOVA test.

In vivo animal studies. Experiments were performed in accordance with the European Commission Directive 2010/63/EU (European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes) and the United Kingdom Home Office (Scientific Procedures) Act 1986 with project approval from the institutional animal welfare and ethical review boards (AWERB). Anaesthesia was induced in adult male Sprague Dawley rats (n = 6 for each time point, 200–300 g) with isoflurane (2–4%; Piramal Healthcare) in pure oxygen (BOC). Animals were placed prone onto a thermo-coupled heating pad (CTC-2–LV; Physequip), and body temperature was maintained at 36.7 °C. Four incisions of 2.5 cm were made: two bilaterally over the spine-trapezius in equal location, and two bilaterally over the medial aspect of the dorsal external oblique. The skin was separated from the muscle with large forceps, and any excess fat was removed. The implants were tunnelled under the skin and placed in direct contact with the muscle, at sites distal to the incision. The order of the implants was randomised but constrained so that each implant appeared in each location at least once, including the PLLA control disc. All rats were implanted with a control material (PLLA). The wounds were sealed with a subcuticular figure of 8 purse string suture with a set-back buried knot using 3-0 polyglyactin sutures (Vicryl—Vicryl Rapide™). The surgical procedure was performed under the strictest of aseptic conditions with the aid of a non-sterile assistant. Post-surgical analgesia was administered, and rats were placed into clean cages with food and water ad libitum. 6 animals were sacrificed at each of the selected time points (4 and 8 weeks).

Histology Studies Samples for histology were collected post-mortem by cutting the area around the polymer implant to obtain tissue samples of ca. 1.5 cm² with the polymer disc in the middle. Samples (n = 6) were then cut in the middle of the polymer disc to get a cross-section of both polymer and tissue, then placed in a 4% PFA solution overnight at 4 °C for fixation. Fixed samples were then washed with increasing % of ethanol (70–100%) followed by 100% xylene before embedding in paraffin. Embedded samples were cut to 5–20-μm thick slices, de-paraffinized in histological grade xylene, rehydrated, and stained with either hematoxylin and eosin (H&E) or Masson’s Trichrome stain, following standard Sigma-Aldrich protocols. Brightfield microscopy was used to examine pathology of select samples (at 4 weeks and 8 weeks), with inflammatory cell load, necrosis presence and capsule thickness analysed at discreet intervals around the sample periphery. Inflammatory scoring was based on ISO 10993 standard scoring (scale range of 0–4, 0 = none, 1 = rare, 2 = mild, 3 = moderate, 4 = severe).

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The authors declare that full experimental details and characterisation of materials are available in the Supplementary Information. All raw data that support the findings in this study are available from the corresponding authors upon request.

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Author contributions

J.C.W., A.P.D. and M.L.B. conceived the material synthesis and designed the project idea. J.C.W. synthesised and characterised the materials. J.C.W., J.Y. and A.C.W. performed thermal and mechanical analyses. T.R.W. conducted AFM analysis under the supervision of R.K.O’R. M.C.A. and A.P.D. designed the in vitro and, with R.T.R.H., in vivo experiments. M.C.A. performed in vitro analyses. M.C.A. and R.T.R.H. performed in vivo experiments while A.C.W. performed the histology. The paper was written through contributions of J.C.W., A.C.W., M.L.B. and A.P.D. All authors have given approval to the final version of the paper.

Competing interests

The authors declare no competing interests.

Additional information

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