WILEY-VCH

Responsive biomaterials: advances in shape memory polymer-based materials

John G. Hardy,* Matteo Palma, Shalom J. Wind, Manus J. Biggs*

Dr. J. G. Hardy

Department of Chemistry, Lancaster University, Lancaster, Lancashire, LA1 4YB, UK.

Materials Science Institute, Lancaster University, Lancaster, Lancashire, LA1 4YB, UK.

E-mail: j.g.hardy@lancaster.ac.uk

Dr. M. Palma

The School of Biological and Chemical Sciences, Queen Mary University of London, Mile

End Road, London, E1 4NS, UK.

Dr. S. J. Wind

Applied Physics and Applied Math, Columbia University, 1020 CEPSR, Mail Code: 8903,

New York, NY 10027, USA.

Dr. M. J. Biggs

Centre for Research in Medical Devices, National University of Ireland Galway, Biosciences

Research Building, Newcastle Road, Dangan. Ireland

E-mail: manus.biggs@nuigalway.ie

1

Shape memory polymers (SMPs) are morphologically responsive materials with potential for a variety of biomedical applications, particularly as devices for minimally invasive surgery and the delivery of therapeutics and cells for tissue engineering, applications which are the focus of this Research News article. A brief introduction to SMPs is followed by a discussion of the scientific community's progress towards the development of SMP-based biomaterials for clinically relevant biomedical applications.

1. Introduction

Shape-memory polymer (SMP)-based materials exist in a 'memorized' macroscopic shape, temporarily exist in another shape and then revert to their original shape upon exposure to a stimulus. These exciting properties render them attractive for a variety of applications in both technical industries (e.g. aeronautics, electronics, textiles) and biomedical industries (e.g. stents, and scaffolds for the delivery of therapeutics and cells).[1]

The application of SMP-based materials for biomedical applications was pioneered by Lendlein and Langer, who first described biodegradable temperature-responsive SMP sutures that tightened and sealed a wound upon the application of heat (41°C), as demonstrated in a rat model (Figure 1).[2] Their work and the emerging work of others has inspired this Research News article.
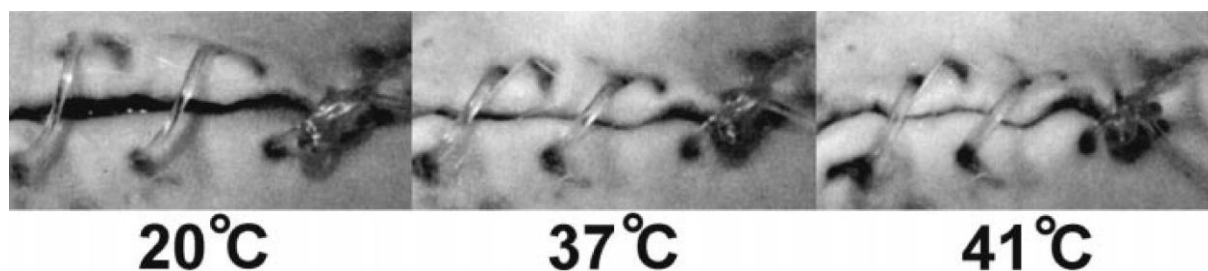
Figure 1. Degradable shape-memory suture for wound closure. The photo series from the animal experiment shows (left to right) the shrinkage of the fiber with increasing temperature. Reproduced with permission.[3] Copyright 2002, The American Association for the Advancement of Science.

The unique morphologically responsive nature of SMP-based materials has the potential to facilitate their application in novel biomedical settings, particularly as devices for minimally invasive surgery, for the delivery of therapeutics and cells and as responsive 'smart' implantable devices. Indeed, by comparison with traditional materials used in medical technologies (e.g. ceramics, metals, polymers) that are morphologically static, SMPs offer a number of potential advantages, the clearest being a significant change in morphology following deployment by simple surgical procedures as exemplified by the work of Lendein and Langer highlighted above. Critically, it can be inferred that SMP devices may be implanted as a simple or densely packed structure which when subjected to a physiological environment will adopt a complex functional three-dimensional morphology. With the alarming rise of antibiotic resistant strains of bacteria that may render previously treatable infections deadly, the importance of simple surgical procedures cannot be overstated both in the developed and developing world, and SMPs offer a means to radically reduce the frequency and severity of infections through the use of keyhole surgery to implant them.

The unique chemical space that SMPs populate offers chemists and chemical engineers significant opportunities to tune their properties to suit a specific application, and many years of fundamental research into this class of polymers has yielded fundamental insight into the structure-function relationships underpinning their function. Indeed, the structure of the polymer backbone plays an important role in SMP hierarchical assembly in 3D, the polymer crosslinking (i.e. chemical/physical crosslinks), and therefore the reversibility and timescale of any shape switching events. Medical SMPs can be engineered to respond to various physiological stimuli (e.g. chemical, electromagnetic, temperature etc.) that result in a physicochemical response of the SMP (i.e. changes in chemical structure, degree of crosslinking and fraction of amorphous/crystalline domains), which can be tailored to produce application-specific changes in polymer morphology. Moreover, the material formulation (films, fibers, foams, gels, particulates) also plays an important role in their task-specific

applications. The excitement that these materials have generated has given rise to a large body of literature (including some systematic studies) of stimuli-responsive SMP-based materials derived from a variety of non-biodegradable and biodegradable polymers (most commonly those that respond to temperature), and we direct interested readers towards a series of excellent reviews of the subject matter.[3]

While a comprehensive review of SMP chemistry (i.e. molecular requirements, mechanism of function, synthesis, their programming, characterization, modeling)[3] is outside the scope of this article, an overview of the stimuli to which SMPs respond may serve to spur their further development for biomedical applications. While the most commonly employed trigger for shape-memory switching is temperature (directly or indirectly applied), it is noteworthy that not all SMPs are body temperature-responsive. In cases where the temperature response of the SMP is above body temperature (e.g.MM5520 thermoplastic polyurethane) it is possible to trigger their shape memory reversion with photothermal excitation as demonstrated for SMP-based stents;[4] the photothermal shape memory response has also been demonstrated with SMPs composites containing gold nanorods as SMP-based sutures, where light-induced heating of the nanorods triggers the SMP-based sutures to change shape and close a wound.[5] Other triggers employed in SMP-based materials include: solvent-polymer interactions (e.g. rehydration), electricity, light (e.g. photoisomerization), magnetism, sound, or indeed chemical stimuli that utilize redox switches, or reversible/dynamic covalent bonds (e.g. acylhydrazones, disulfides) and non-covalent bonds (e.g. supramolecular interactions, hydrogen bonds) engineered into the polymers.[3] Clearly, the successful translation of SMP-based materials from the laboratory to the clinic relies on their ability to respond to biocompatible triggering events, and examples of progress in this direction are highlighted below.

2. SMP-based medical devices

2.1. SMP-based stents

Stents based on temperature-responsive polyurethanes (and drugs with undisclosed structures) were some of the earliest examples of SMP-based medical devices studied *in vitro*, wherein the shape memory of these materials exhibited at body temperature could help to fix a device in place *in vivo*.[6] The first examples of fully biodegradable body temperature-responsive SMP stents were based on poly(L-lactic acid) (PLLA) and poly(glycolic acid) (PLGA) bilayers.[7] Stents based on shape memory copolymers (with blocks of polycaprolactone and a microbial polyester) showed complete self-expansion at body temperature within 25 seconds.[8] Stents based on poly(*t*-butyl acrylate) crosslinked with poly(ethylene glycol) dimethacrylate were shown to be body temperature responsive; and the time for full recovery (1-10 minutes) from storage at room temperature could be controlled by tuning the crosslink density of the polymer and porosity of the stent.[9] SMPs that respond swiftly to temperature changes have been shown to decrease surgery times from minutes to seconds for certain minimally invasive surgical procedures; as demonstrated using SMPs (copolymers of *t*-butyl acrylate and *n*-butyl acrylate crosslinked with poly(ethylene glycol) dimethacrylate) that were coated on poly(ethylene terephthalate) meshes and delivered laparoscopically *in vivo* in a pig model, reinforcing the importance of developing such swiftly responding materials.[10] Analogous SMP-coated meshes implanted in rats were shown to deter the infiltration/migration of inflammatory cells and fibroblasts relative to uncoated poly(ethylene terephthalate) meshes because the interstitial space in spaces in the poly(ethylene terephthalate) meshes was not patent, resulting in the deposition of less collagenous scar tissue deposited around the SMP-coated meshes than the uncoated poly(ethylene terephthalate) meshes.[11]

Critically, responsive stents that prevent/deter restenosis (narrowing of blood vessels after surgical interventions) are a significant focus of SMP technology. Examples of SMP-derived stents include temperature-responsive devices that elute sirolimus (a drug with

antiproliferative and immune suppressive properties),[12] or paclitaxel (an antiproliferative that limits the growth of neointima)[13] over a period of weeks. Interestingly, temperature-responsive SMP-based stents that elute curcumin (an antiproliferative and anticoagulant) and mitomycin C (an inhibitor of smooth muscle cell proliferation and neointima formation) over 14 and 60 days, respectively, were shown to simultaneously inhibit early thrombosis and long term smooth muscle cell proliferation, which are promising for the prevention of restenosis.[14]

A particularly interesting example of a body-temperature-responsive SMP-based stent is intended for use in patients suffering from esophageal stricture (sometimes induced by cancer or trauma), based on a copolymer of poly(caprolactone-co-DL-lactide). Such SMP-based stents have prospects for the replacement of metal alloy-based stents displaying shape memory properties because their mechanical properties are closer to those of the tissue in which they are implanted, and preclinical experiments using dogs have successfully demonstrated their potential advantage over traditional metallic devices.[15]

2.2. SMP-based materials with speculative application as medical devices

As noted above, the presence of microbes on implant surfaces can cause life-threatening infections (particularly with the alarming rise in prevalence of antimicrobial resistant strains). Consequently, a variety of SMP-based devices have been developed, some of which display antimicrobial activity. Indeed, SMPs loaded with Fe_3O_4 nanoparticles (which can trigger shape-memory effects through inductive heating)[16] were shown to display antimicrobial activity towards *Staphylococcus aureus* and *Klebsiella pneumoniae*,[17] and SMPs loaded with silver nanoparticles were also shown to display antimicrobial activity towards *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[18]

Therapeutic embolization entails deliberately blocking a blood vessel (e.g. clipping an aneurysm to prevent internal bleeding, or reducing/stopping blood flow to tumors), and body temperature-responsive poly(ether urethane) SMP-based foams have been shown to be

cytocompatible and enable the infiltration of mouse L929 fibroblast cells *in vitro* which is promising for potential future applications as aneurysm fillers *in vivo*.[19] Different temperature-responsive polyurethane SMPs that responded to temperature by expanding up to 70 times their original volume were shown to be relatively non-immunogenic *in vitro*[20] and after 90 days of implantation of radio-opaque analogues in a pig aneurysm model these materials showed low inflammation and good healing responses.[21]

3. SMP-based drug delivery devices

3.1. SMP-based hydrogels as drug delivery devices

Hydrogels are widely used in drug delivery because of their tunable compositions, crosslinking densities, and the molecular weight distribution of drugs that can be delivered in a controlled manner. One of the earliest examples of SMP-based devices designed for drug delivery was reported by Uragami and coworkers.[22] Non-biodegradable polyacrylamide hydrogels incorporating supramolecular crosslinks formed through the specific interaction of an antibody and antigen attached to the backbone of the polyacrylamide chains were observed to swell upon the addition of competitive antigen to the hydrogel, enabling the delivery of a high molecular weight model drug (hemoglobin, 68 kDa) from the hydrogel matrix within a few hours.[22] Supramolecular polymer-based hydrogels displaying pH-responsive SMP properties, have also been developed to allow the passive diffusion of anionic species at low pH (3.2) and the delivery of cationic species, triggered by an increase in pH (to 6.2).[23] Alternatively, shape memory coatings for model drug-loaded hydrogels have been demonstrated to be effective for inducing hydrogel-medicated drug delivery resulting from the stress induced by the shape memory outer layer following an increase in temperature.[24]

Hydration-responsive SMP-based materials enable the delivery of drugs and potentially cells to a precise location inside the body by minimally invasive surgical procedures. For example, xerogels based on composites of bacterial nanocellulose with various hydrophilic additives

(e.g. glucose, sucrose, lactose, polyethylene glycol, sodium chloride) have been shown to respond to rehydration by releasing a model low molecular weight drug azorubine over a period of hours.[25] Furthermore, macroporous alginate hydrogel scaffolds were introduced into immunocompromised mice through a small catheter, and were rehydrated in situ with a suspension of cells (primary bovine articular chondrocytes) or cell-free medium delivered through the same catheter. The scaffolds typically recovered their original shape and size within one hour of implantation, maintained the structure of the original scaffold after 2 months and appeared histologically stable after 6 months in vivo.[26] Analogous alginate-based scaffolds were also shown to allow the adhesion and growth of stem cells *in vitro*, and to be capable of controlled release of insulin-like growth factor-1[27] or macromolecular model drugs *in vivo* when implanted subcutaneously in a mouse model.[28]

3.2. SMP-based materials with speculative application as drug delivery devices

SMP-based particulate systems are also being widely explored, for drug delivery applications in vivo. Indeed, temperature-responsive biodegradable poly(DL-lactic acid)-based particles are capable of delivering the low molecular weight drug theophylline.[29] More recently, temperature-responsive particles composed of biodegradable copolymers of poly(ω-pentadecalactone) and polycaprolactone have demonstrated the ability to be switched from oblate spheroid to prolate spheroid (**Figure 2**).[30] Analogous temperature-responsive particles composed of polycaprolactone and poly(ethylene glycol) have been shown to be phagocytosed by macrophages and were subsequently switched from spherical to ellipsoidal. In this study the authors suggested that it would be possible to either promote or deter phagocytosis in future studies employing iterations of these particles.[31]
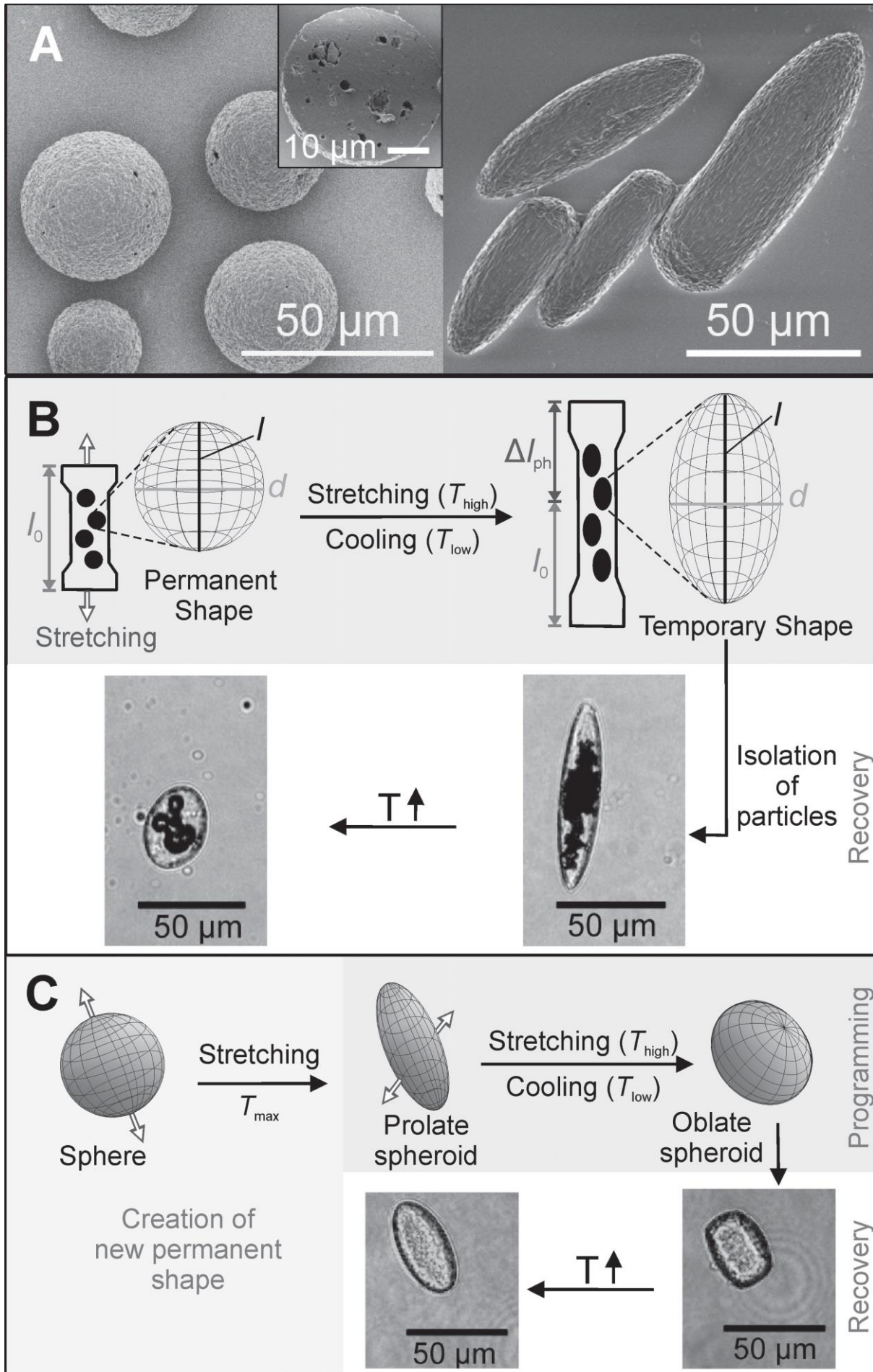
Figure 2. SME of micrometer-sized particles. (A) SEM images of particles in their permanent spherical shape (left) and programmed prolate ellipsoidal shape (right). (B) Programming of spherical particles (permanent shape) embedded in PVA phantoms (l_0 = initial length, Δl_{ph} = length change during stretching; $\Delta l_{ph} \cdot l_0^{-1} = \varepsilon_{ph}$) to their temporary shape and microscopy of temperature induced shape recovery for isolated particles (ε_{ph} = 100%). (C) Shape recovery to non-spherical shape after i) heating to $T_{max} > T_{m,PPDL}$, stretching (ε_{ph} = 50%), and cooling for defining the new permanent prolate spheroidal shape, and ii) programming in perpendicular direction (ε_{ph} = 50%) at T_{high} to temporary oblate spheroidal shape. Reproduced with permission.[30] Copyright 2014, Wiley.

Temperature-responsive composites-based on polycaprolactone and poly(sebacic anhydride), have been shown to be capable of delivering paracetamol (5 weight % loading) by passive diffusion while maintaining their SMP properties,[32] and ultrasound-responsive SMP-based drug delivery devices have been developed for the delivery of copper sulfate (formerly used as an emetic and antimalarial),[31] or a high molecular weight model drug (lysozyme),[33] which may find application in the emerging area of ultrasound-mediated drug delivery systems.[34]

Lendlein and coworkers have made some interesting contributions to the literature with temperature-responsive degradable caprolactone-based polymers for the delivery of hydrophilic drugs (such as ethacridine lactate) and hydrophobic drugs (e.g. Enoxacin).[35] They further developed these systems to act as implantable devices with body temperature induced shape change (potentially enabling immobilization in a fixed location in a patient), enabling the delivery of ethacridine lactate, Enoxacin and Nitrofurantoin,[36] and these systems were shown to slowly degrade over the period of weeks when implanted in rats.[37] Subsequently, other researchers have manufactured body temperature responsive SMP device that immobilized a drug delivery device, for the delivery of model macromolecular drugs to the vagina, as demonstrated *in vivo* in a rabbit model.[38]

4. SMP-based biomaterials for tissue engineering

4.1. Generic SMP-based tissue scaffolds

SMP-based tissue scaffolds potentially enable their implantation via minimally-invasive surgical techniques, and are of broad applicability in the body, with examples of both soft and hard tissue scaffolds having been reported. The ubiquity of fibroblasts makes them very popular for preliminary *in vitro* studies on SMP-based materials. Indeed, Lendlein and Langer's biodegradable temperature-responsive SMPs that were used as sutures for wounds[2] were shown to support the adhesion and proliferation of mouse fibroblast NIH 3T3 cells over a period of one week,[39] and films composed of temperature-responsive poly(glycerol-co-dodecanoate) SMPs have been shown to support the adhesion and proliferation of human fibroblast cells over a period of three weeks.[40] Studies involving stem cells and temperature-responsive SMPs based on polycaprolactone have been shown to support the adhesion and proliferation of human bone marrow-derived stem cells over a period of 3 days.[41] More advanced studies have focused on the development of biomaterials with higher technology readiness levels tend to include *in vivo* studies in small mammals. For example, temperature-responsive potato starch-derived SMP-based fibers implanted in a rat model exhibited normal tissue integration with a low inflammatory response after 8 days.[42] Interestingly, biodegradable temperature-responsive SMPs based on copolymers of polyhedral oligomeric silsesquioxane and poly(D,L-lactide) implanted subcutaneously in a rat model elicited a mild foreign body type immune response, their degradation rates inversely correlated with the length of the poly(D,L-lactide) chains, and one year after implantation no pathologic abnormities were detected from the vital/scavenger organs examined, highlighting their promise for scaffold-assisted tissue repair.[43]

4.2. Instructive SMP-based tissue scaffolds

Tissue scaffolds that instruct cell behaviour represent a significant focus of current tissue engineering strategies.[44] Films composed of temperature-responsive caprolactone-based SMPs have been shown to support the adhesion and proliferation of mouse fibroblast L929

cells over a period of one week.[45] Subsequent studies on similar temperature-responsive caprolactone-based SMPs have reported the adhesion and proliferation of mouse fibroblast L929 cells, rat mesothelial cells, human mesothelial cells and human mesenchymal stem cells on the materials for up to 3 weeks. However, activation of the shape memory effect by heating to 54°C was shown to affect L929 cell adhesion and induce apoptosis (although not necrosis). Control studies showed that these effects was not through cellular exposure to elevated temperature, but were rather related to the shape change process,[46] which may provide mechanical stimulation to prevent adhesion or promote cell death. Body temperature-responsive SMP-based materials that are programmed to change surface topography can also be used to control cell morphology. Indeed, films with micrometer-scale grooves that act as topographical cues have been explored as active materials to induce mouse embryonic fibroblasts to alignment. These SMP substrates can be switched from anisotropic topographies to induce contact guidance to flat featureless surface wherein loss of the topographical cue leads to a decrease in cell alignment (as evidenced by an increase in angular dispersion while maintaining cell viability);[47] an analogous effect is observed for human adipose-derived stem cells that align on aligned electrospun SMP fibers and lose their alignment after the scaffold is triggered to switch to unaligned fibers.[48] Elegant experiments showed that SMP-based films with micrometer-scale grooves programmed to switch their alignment by 90° induced mouse fibroblast NIH 3T3 cells to realign with the grooves over the period of 48 hours.[49] Furthermore, analogous systems with grooves with switchable widths have been employed to apply mechanical force to regulate the shape and the cytoskeletal arrangement of rat stem cells, thereby coaxing lineage-specific differentiation of the stem cell towards myogenic lineages in the absence of any induction factors.[50] Taken together, this hints that SMP topographies may play important future roles in smart, tissue engineered implants, or lab-on-chip devices.

4.3. SMP-based vascular tissue scaffolds

Lendlein's group have further developed SMP-based materials for vascular tissue regeneration, studying a variety of SMPs, and exploring processing parameters for the fabrication of various material formulations. Their studies have employed block copolymer SMPs based on poly(p-dioxanone)diol and poly(ε-caprolactone)diol (PDCs), which have been shown to enable adhesion of endothelial cells,[51] to be hemocompatible to capillary endothelial cells in the chorioallantois membrane (CAM) test,[51] and to be angiogenic.[51, 52] When compared to polypropylene (widely used for blood-contacting medical devices such as blood oxygenators and dialysis tubes), protein adsorption studies showed higher amounts of blood plasma proteins adsorbed on PDC.[53] Plasma kallikrein synthesis was unchanged on PDC and polypropylene, however, platelet adhesion on PDC materials was markedly lower than on polypropylene, suggesting a reduced thrombogenic potential with implications for vascular tissue engineering.[53]

4.4. SMP-based bone tissue scaffolds

The development of SMP-based bone-tissue scaffolds has become a focus of recent research due to the discovery of responsive bioglass formulations and polymeric nanocoposites with high compression resistance. The benefit of SMP in orthopedic applications stem from an ability of these materials to expand into irregular bone defects to promote fixation and regeneration. Interestingly, hydration-responsive chitosan-bioglass composite tissue scaffolds have been shown to rapidly fill bone defects in vivo,[54] as have body temperature-responsive copolymers of L-lactide/glycolide/trimethylene carbonate or L-lactide/glycolide/e-caprolactone (Figure 3).[55] Electrospun mats of temperature-responsive biodegradable SMPs based on poly(D,L-lactide-co-trimethylene carbonate) have also demonstrated to support rat calvarial osteoblast adhesion and proliferation, and functionally promote biomineralization-relevant alkaline phosphatase expression and mineral deposition *in vitro*.[56]
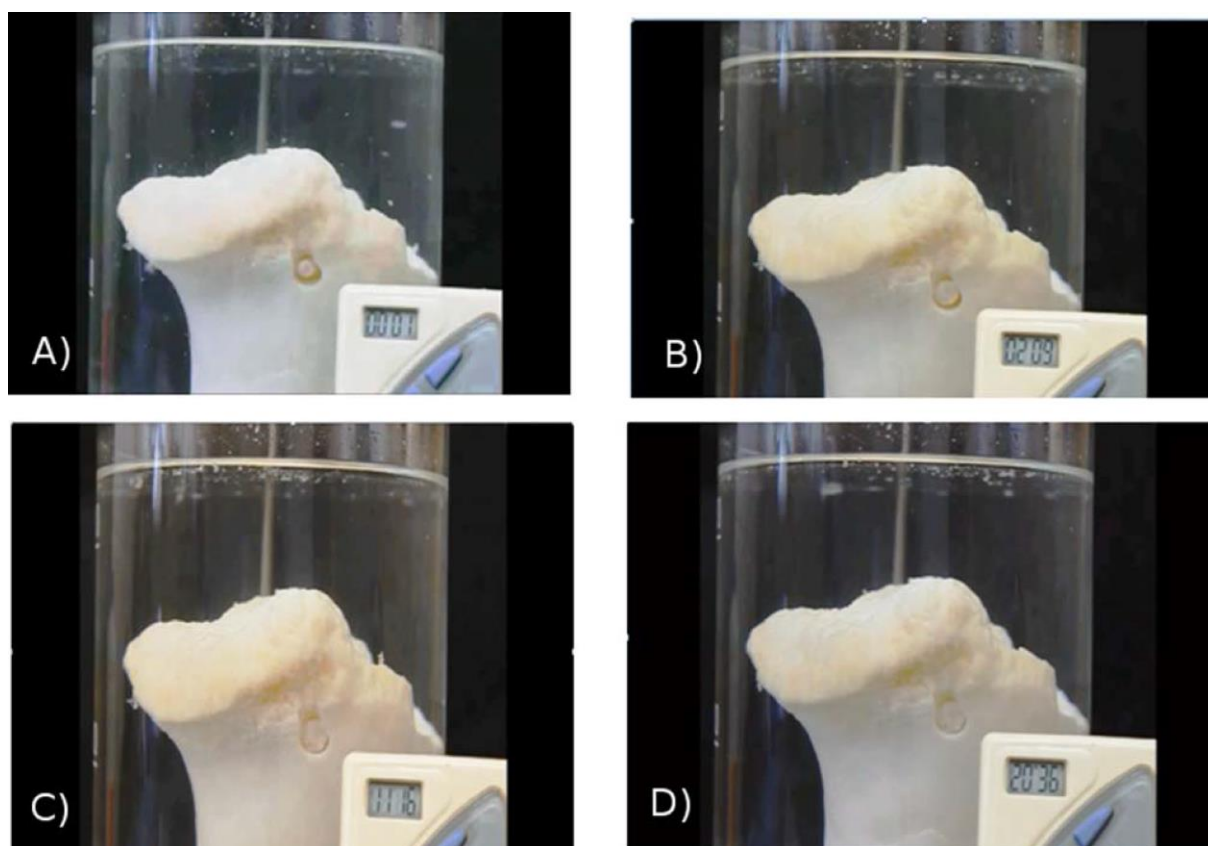
Figure 3. Pictures presenting the filling process of bone defect with scaffold no. 1 in model bone tissue defect: (A) after few seconds, (B) after 2 min, (C) after 11 min and (D) after 20 min from application. Test was performed in water bath at 37°C. Reproduced with permission.[55] Copyright 2014, Wiley.

Importantly, temperature-responsive polycaprolactone-based foams (with an optional bioactive polydopamine coating) are reported to become malleable when warm and could be pressed into an irregular model bone defect, and locked within the defect when cooled. These materials promoted adhesion, proliferation, osteogenic gene expression and extracellular matrix deposition when cultured with human osteoblasts *in vitro*.[57] Furthermore, Composite materials incorporating hydroxyapatite are commonplace in bone tissue engineering studies, and composites of poly(D,L-lactide) and hydroxyapatite have been reported to display temperature-responsive shape memory properties.[58] Studies employing temperature-responsive foams based on composites of polycaprolactone and hydroxyapatite showed that they were capable of controlled release of bone morphogenetic protein-2 and displayed good

cytocompatibility towards rabbit bone marrow-derived stem cells *in vitro*. Critically, when implanted in a rabbit mandibular bone defect this material was shown to promote new bone generation after 8 weeks.[59]


5. Conclusion

SMP-based materials (**Figure 4**) represent a novel class of biomaterials with potential for biomedical applications including devices employable via minimally invasive surgery or devices for the delivery of drugs and cells, as highlighted in this Research News article.

We see many challenges that first need to be overcome in terms of the development of polymer chemistry (e.g. designing polymers that respond to biocompatible triggers, potentially even endogenous biological conditions/events); materials processing (e.g. obtaining materials with biomimetic mechanical properties and topographical properties); biocompatibility (e.g. biodegradation into safe non-toxic byproducts), preclinical testing (ideally without the use of animals), and ultimately clinical trials (which requires the technology to offer strategic advantages over others on the market at an affordable price).

We foresee that these materials have strong prospects for clinical translation, particularly when attractive multifunctional properties have been engineered into the polymers (e.g. biodegradable antimicrobial polymers), however, we believe that such materials have prospects for grand healthcare challenges such as the provision of affordable healthcare technologies in both the developed and developing world.
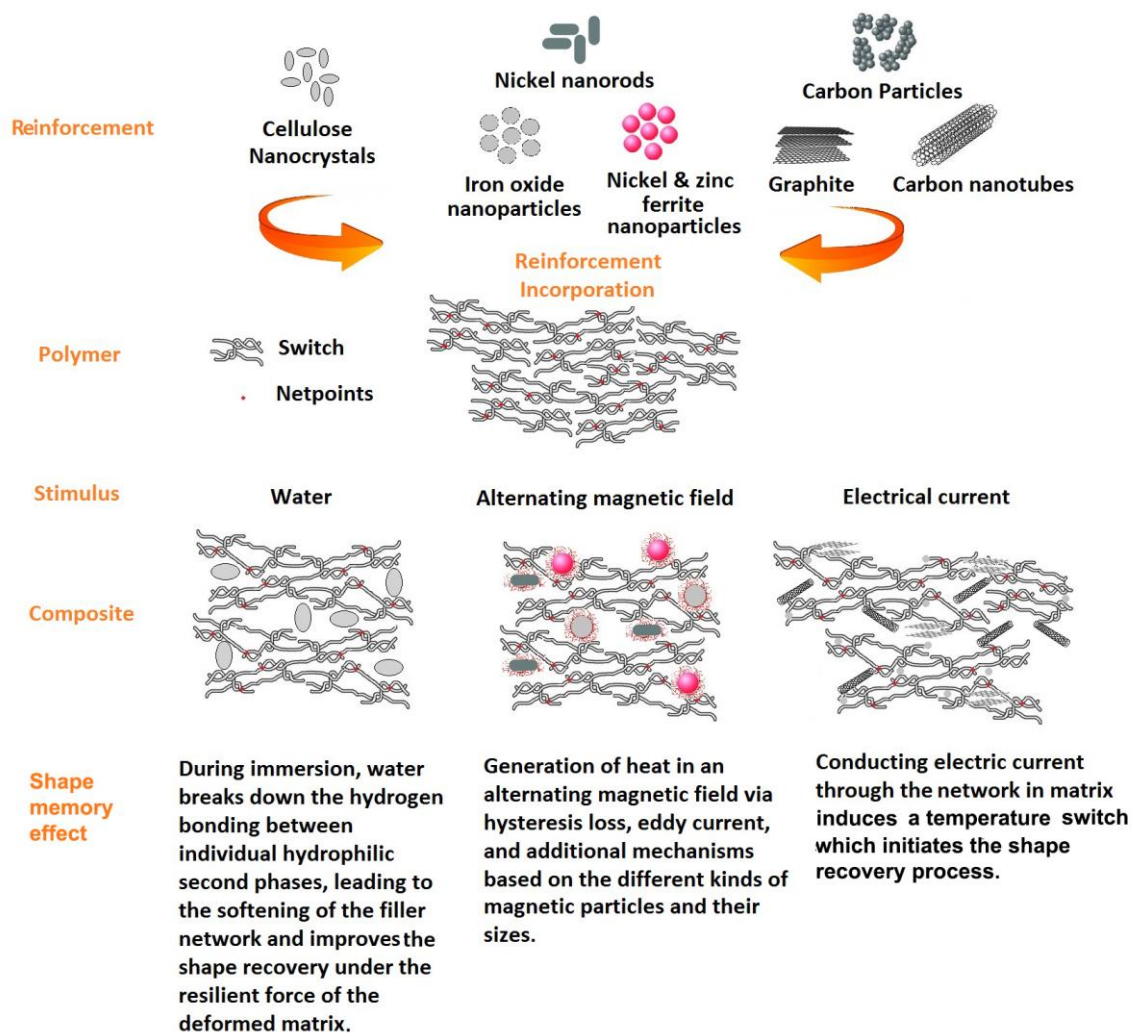
Figure 4. Schematic overview of the shape memory process in nanocomposite polymeric materials. Nanoparticulates enhance the polymer relaxation through localized effects on the polymer netpoints.

[1]   ((Journal articles)) a) A. B. Author 1, C. D. Author 2, *Adv. Mater.* **2006**, *18*, 1; b) A. Author 1, B. Author 2, *Adv. Funct. Mater.* **2006**, *16*, 1.

[2]   ((Work accepted)) A. B. Author 1, C. D. Author 2, *Macromol. Rapid Commun.*, DOI: 10.1002/marc.#########.

[3]   ((Books)) H. R. Allcock, *Introduction to Materials Chemistry*, Wiley, Hoboken, NJ, USA **2008**.

[4]   ((Edited books or proceedings volumes)) J. W. Grate, G. C. Frye, in *Sensors Update*, Vol. 2 (Eds: H. Baltes, W. Göpel, J. Hesse), Wiley-VCH, Weinheim, Germany **1996**, Ch. 2.

[5]   ((Presentation at a conference, proceeding not published)) Author, presented at Abbrev. Conf. Title, Location of Conference, Date of Conference ((Month, **Year**)).

[6]   ((Thesis)) Author, *Degree Thesis*, University (location if not obvious), Month, **Year**.

[7]   ((Patents)) a) A. B. Author 1, C. D. Author 2 (Company), *Country Patent Number*, **Year**; b) W. Lehmann, H. Rinke (Bayer AG) *Ger. 838217*, **1952**.

[8]   ((Website)) Author, Short description or title, URL, accessed: Month, Year.

[9]   …((Please include all authors, and do not use "et al."))

Stimuli-responsive shape memory polymer-based materials have great potential for application in a variety of biomedical applications. Their development towards use as functional biomedical devices for drug delivery, minimally invasive surgery and tissue engineering are the focus of this Research News article, particularly with a view to their progress towards clinical relevance.

Keywords: shape memory polymers, biomaterials, drug delivery, tissue engineering, minimally invasive surgeries

J. G. Hardy,* M. Palma, S. J. Wind, M. J. Biggs*

Responsive biomaterials: advances in shape memory polymer-based materials

ToC figure ((Please choose one size: 55 mm broad × 50 mm high **or** 110 mm broad × 20 mm high. Please do not use any other dimensions))

[1] L. Sun, W. M. Huang, Z. Ding, Y. Zhao, C. C. Wang, H. Purnawali, C. Tang, Mater Design 2012, 33, 577.

[2] A. Lendlein, A. M. Schmidt, R. Langer, P Natl Acad Sci USA 2001, 98, 842; A. Lendlein, R. Langer, Science 2002, 296, 1673.

[3] G. J. Berg, M. K. McBride, C. Wang, C. N. Bowman, Polymer 2014, 55, 5849; A. S. Hoffman, Adv Drug Deliver Rev 2013, 65, 10; Q. H. Meng, J. L. Hu, Compos Part a-Appl S 2009, 40, 1661; Q. Zhao, H. J. Qi, T. Xie, Prog Polym Sci 2015, 49-50, 79; M. D. Hager, S. Bode, C. Weber, U. S. Schubert, Prog Polym Sci 2015, 49-50, 3; J. S. Leng, X. Lan, Y. J. Liu, S. Y. Du, Prog Mater Sci 2011, 56, 1077; J. L. Hu, Y. Zhu, H. H. Huang, J. Lu, Prog Polym Sci 2012, 37, 1720.

[4] G. M. Baer, W. Small, T. S. Wilson, W. J. Benett, D. L. Matthews, J. Hartman, D. J. Maitland, Biomed Eng Online 2007, 6.

[5] K. C. Hribar, R. B. Metter, J. L. Ifkovits, T. Troxler, J. A. Burdick, Small 2009, 5, 1830.

[6] H. M. Wache, D. J. Tartakowska, A. Hentrich, M. H. Wagner, J Mater Sci-Mater M 2003, 14, 109.

[7] S. S. Venkatraman, L. P. Tan, J. F. D. Joso, Y. C. F. Boey, X. T. Wang, Biomaterials 2006, 27, 1573.

[8] L. A. Xue, S. Y. Dai, Z. Li, Biomaterials 2010, 31, 8132.

[9] C. M. Yakacki, R. Shandas, C. Lanning, B. Rech, A. Eckstein, K. Gall, Biomaterials 2007, 28, 2255.

[10] M. M. Zimkowski, M. E. Rentschler, J. Schoen, B. A. Rech, N. Mandava, R. Shandas, J Biomed Mater Res A 2013, 101, 2613.

[11] M. M. Zimkowski, M. E. Rentschler, J. A. Schoen, N. Mandava, R. Shandas, J Biomed Mater Res B 2014, 102, 1093.

[12] J. Jaworska, K. Jelonek, M. Sobota, J. Kasperczyk, P. Dobrzynski, M. Musial-Kulik, A. Smola-Dmochowska, H. Janeczek, B. Jarzabek, J Appl Polym Sci 2015, 132.

[13] M. Musial-Kulik, J. Kasperczyk, A. Smola, P. Dobrzynski, Int J Pharmaceut 2014, 465, 291.

[14] C. S. Yang, H. C. Wu, J. S. Sun, H. M. Hsiao, T. W. Wang, Acs Appl Mater Inter 2013, 5, 10985.

[15] X. Yu, L. Wang, M. Huang, T. Gong, W. Li, Y. Cao, D. Ji, P. Wang, J. Wang, S. Zhou, Journal of materials science. Materials in medicine 2012, 23, 581.

[16] X. T. Zheng, S. B. Zhou, Y. Xiao, X. J. Yu, X. H. Li, P. Z. Wu, Colloid Surface B 2009, 71, 67.

[17] N. Tran, A. Mir, D. Mallik, A. Sinha, S. Nayar, T. J. Webster, Int J Nanomed 2010, 5, 277; B. Das, M. Mandal, A. Upadhyay, P. Chattopadhyay, N. Karak, Biomed Mater 2013, 8.

[18] A. Soto-Quintero, A. Meneses-Acosta, A. Romo-Uribe, Eur Polym J 2015, 70, 1.

[19] L. De Nardo, R. Alberti, A. Cigada, L. Yahia, M. C. Tanzi, S. Fare, Acta Biomater 2009, 5, 1508.

[20] P. Singhal, J. N. Rodriguez, W. Small, S. Eagleston, J. V. de Water, D. J. Maitland, T. S. Wilson, J Polym Sci Pol Phys 2012, 50, 724.

[21] J. N. Rodriguez, Y. J. Yu, M. W. Miller, T. S. Wilson, J. Hartman, F. J. Clubb, B. Gentry, D. J. Maitland, Ann Biomed Eng 2012, 40, 883; P. Singhal, W. Small, E. Cosgriff-Hernandez, D. J. Maitland, T. S. Wilson, Acta Biomater 2014, 10, 67.

[22] T. Miyata, N. Asami, T. Uragami, Nature 1999, 399, 766.

[23] L. Qin, F. Xie, P. F. Duan, M. H. Liu, Chem-Eur J 2014, 20, 15419.

[24] G. Ozaydin-Ince, K. K. Gleason, M. C. Demirel, Soft Matter 2011, 7, 638.

[25] A. Muller, M. Zink, N. Hessler, F. Wesarg, F. A. Muller, D. Kralisch, D. Fischer, Rsc Adv 2014, 4, 57173.

[26] A. J. Thornton, E. Alsberg, M. Albertelli, D. J. Mooney, Transplantation 2004, 77, 1798; A. J. Thornton, E. Alsberg, E. E. Hill, D. J. Mooney, J Urology 2004, 172, 763.

[27] L. Wang, J. Shansky, C. Borselli, D. Mooney, H. Vandenburgh, Tissue Eng Pt A 2012, 18, 2000.

[28] S. A. Bencherif, R. W. Sands, D. Bhatta, P. Arany, C. S. Verbeke, D. A. Edwards, D. J. Mooney, P Natl Acad Sci USA 2012, 109, 19590.

[29] R. Steendam, M. J. van Steenbergen, W. E. Hennink, H. W. Frijlink, C. F. Lerk, J Control Release 2001, 70, 71.

[30] C. Wischke, M. Schossig, A. Lendlein, Small 2014, 10, 83.

[31] T. Gong, K. Zhao, W. X. Wang, H. M. Chen, L. Wang, S. B. Zhou, J Mater Chem B 2014, 2, 6855.

[32] Y. Xiao, S. B. Zhou, L. Wang, X. T. Zheng, T. Gong, Compos Part B-Eng 2010, 41, 537.

[33] M. Bao, Q. H. Zhou, W. Dong, X. X. Lou, Y. Z. Zhang, Biomacromolecules 2013, 14, 1971.

[34] G. A. Husseini, W. G. Pitt, Adv Drug Deliver Rev 2008, 60, 1137.

[35] A. T. Neffe, B. D. Hanh, S. Steuer, A. Lendlein, Adv Mater 2009, 21, 3394.

[36] C. Wischke, A. T. Neffe, S. Steuer, A. Lendlein, J Control Release 2009, 138, 243; C. Wischke, A. T. Neffe, S. Steuer, A. Lendlein, Eur J Pharm Sci 2010, 41, 136.

[37] C. Wischke, A. T. Neffe, S. Steuer, E. Engelhardt, A. Lendlein, Macromol Biosci 2010, 10, 1063.

[38] R. S. Teller, R. Rastogi, T. J. Johnson, M. J. Blair, R. W. Hitchcock, P. F. Kiser, Pharm Res-Dordr 2014, 31, 2344.

[39] S. G. Xu, P. Zhang, G. M. Zhu, Y. M. Jiang, J Mater Eng Perform 2011, 20, 807.

[40] F. Migneco, Y. C. Huang, R. K. Birla, S. J. Hollister, Biomaterials 2009, 30, 6479.

[41] X. W. Yang, C. Z. Cui, Z. X. Tong, C. R. Sabanayagam, X. Q. Jia, Acta Biomater 2013, 9, 8232.

[42] A. Beilvert, F. Chaubet, L. Chaunier, S. Guilois, G. Pavon-Djavid, D. Letourneur, A. Meddahi-Pelle, D. Lourdin, Carbohyd Polym 2014, 99, 242.

[43] T. M. Filion, J. W. Xu, M. L. Prasad, J. Song, Biomaterials 2011, 32, 985.

[44] M. P. Lutolf, J. A. Hubbell, Nat Biotechnol 2005, 23, 47.

[45] D. Rickert, A. Lendlein, A. M. Schmidt, S. Kelch, W. Roehlke, R. Fuhrmann, R. P. Franke, J Biomed Mater Res B 2003, 67B, 722.

[46] S. Neuss, I. Blomenkamp, R. Stainforth, D. Boltersdorf, M. Jansen, N. Butz, A. Perez-Bouza, R. Knuchel, Biomaterials 2009, 30, 1697.

[47] K. A. Davis, K. A. Burke, P. T. Mather, J. H. Henderson, Biomaterials 2011, 32, 2285.

[48] L. F. Tseng, P. T. Mather, J. H. Henderson, Acta Biomater 2013, 9, 8790.

[49] M. Ebara, K. Uto, N. Idota, J. M. Hoffman, T. Aoyagi, Int J Nanomed 2014, 9, 117.

[50] T. Gong, K. Zhao, G. Yang, J. R. Li, H. M. Chen, Y. P. Chen, S. B. Zhou, Advanced healthcare materials 2014, 3, 1608.

[51] D. Rickert, M. A. Moses, A. Lendlein, S. Kelch, R. P. Franke, Clin Hemorheol Micro 2003, 28, 175.

[52] B. Hiebl, C. Mrowietz, J. Goers, M. Bahramsoltani, J. Plendl, K. Kratz, A. Lendlein, F. Jung, Clin Hemorheol Micro 2010, 46, 233.

[53] R. Tzoneva, B. Seifert, M. Behl, A. Lendlein, Clin Hemorheol Micro 2012, 52, 337.

[54] C. O. Correia, A. J. Leite, J. F. Mano, Carbohyd Polym 2015, 123, 39.

[55] P. Rychter, E. Pamula, A. Orchel, U. Posadowska, M. Krok-Borkowicz, A. Kaps, N. Smigiel-Gac, A. Smola, J. Kasperczyk, W. Prochwicz, P. Dobrzynski, J Biomed Mater Res A 2015, 103, 3503.

[56]   M. Bao, X. X. Lou, Q. H. Zhou, W. Dong, H. H. Yuan, Y. Z. Zhang, Acs Appl Mater Inter 2014, 6, 2611.

[57]   D. W. Zhang, O. J. George, K. M. Petersen, A. C. Jimenez-Vergara, M. S. Hahn, M. A. Grunlan, Acta Biomater 2014, 10, 4597.

[58]   X. T. Zheng, S. B. Zhou, X. H. Li, H. Weng, Biomaterials 2006, 27, 4288.

[59]   X. Liu, K. Zhao, T. Gong, J. Song, C. Y. Bao, E. Luo, J. Weng, S. B. Zhou, Biomacromolecules 2014, 15, 1019.