POLYMER CHEMISTRY

# Still in control

The development of synthetic strategies enabling the fabrication of well-defined polymer–biomolecule conjugates, together with advances in top-down nanofabrication, are two highlights from a recent meeting of polymer scientists.

Jeffrey Pyun

The design of polymeric materials with useful and tunable properties continues to be critical in existing and emerging technologies. Advances in polymer chemistry spanning new polymerization and functionalization methods have enabled the preparation of complex, multifunctional materials. As a result, polymer science has impacted numerous areas such as supramolecular chemistry, nanotechnology, biomaterials, energy and sustainable materials. This influence was evident in the diverse range of topics, from fundamental to applied technological problems, discussed at the Warwick 2012 Polymers conference in July.

Joseph DeSimone (University of North Carolina) described developments in top-down nanofabrication to create polymeric microparticles and nanoparticles of various shapes, sizes and compositions. This process, termed particle replication in non-wetting templates (PRINT), uses crosslinkable perfluoropolyethers to create low surface energy, chemically resistant moulds and replicas for nanoimprint lithography[1]. These PRINT particles can be prepared in appreciable quantities using roll-to-roll processing methods. A major thrust of the DeSimone group is the use of PRINT particles for biomedical applications — as vehicles for drug delivery, short interfering RNA (siRNA) delivery, prodrug incorporation, and combined chemotherapy and imaging capabilities[2,3]. In the realm of materials chemistry, the PRINT process has been used to generate mesoscopic analogues to synthetic macromolecules, termed mesopolymers, which are composed of one-dimensional polymeric materials. Recent efforts have generated segmented mesopolymers with an ABA-triblock composition that incorporates discrete hydrophilic and hydrophobic segments in each block (Fig. 1a)[4]. Using the same technique, DeSimone and colleagues could also make rod-like particles that contain one polymeric component, diblock and multiblock systems. The mesoscopic ABA-triblock particles self-assemble at a water/oil interface to form ordered ribbon structures (Fig. 1b). This side-to-side aggregation is a consequence of enthalpic associations between the different polymeric segments — presenting a mesoscopic analogue to self-organization observed on the molecular length scale within block copolymer and micellar systems.

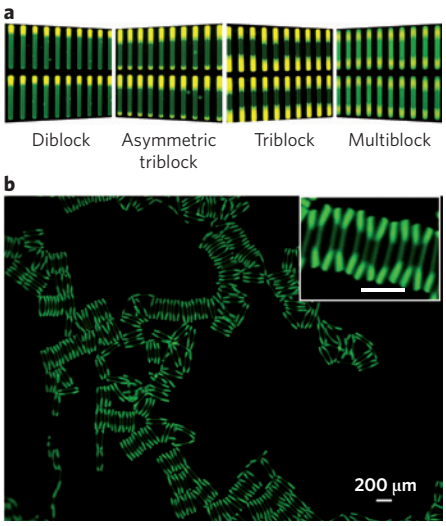


**Figure 1 |** Multiphase rod-like particles fabricated using the PRINT processing method. **a**, Fluorescence microscopy images of arrays of 20 × 20 × 240 μm rod-like particles on a harvesting film with tunable dimensions in AB-diblock, asymmetric diblock, ABA-triblock and multiblock configurations. **b**, Fluorescence microscopic image of ABA-triblock particles assembled at the water/oil interface. Inset: higher magnification image clearly showing the side-by-side aggregation of the particles. Scale bar, 200 μm. Image reproduced with permission from ref. 4, © 2012 ACS.

On a different note, controlled radical polymerization (CRP) proved to be a widely used tool for the research presented at the conference. The field of CRP, since its inception in the 1990s[5], has seen the rise of systems including atom transfer radical polymerization (ATRP) and reversible addition-fragmentation chain transfer (RAFT) polymerization for the preparation of well-defined free radically derived polymers. Kris Matyjaszewski (Carnegie Mellon University), a leading expert on ATRP, discussed developments in CRP. At the heart of his efforts has been the quest for the ideal catalytic system, which has spawned improvements on ATRP, such as activator generated by electron transfer (AGET) ATRP (ref. 6). These new catalytic systems have been largely successful in the stabilization of catalysts in different media and reducing transition metal loadings to parts-per-million quantities. With these techniques, ATRP can now be conducted under biologically relevant conditions and implemented for the modification of biomolecules such as proteins. This can be achieved by two different methods; first, 'grafting from', in which a polymer grows from an initiating site on the biomolecule, and second, 'grafting to', which involves a preformed polymer with a reactive chain end combining with a functional group on the biomolecule. Matyjaszewski described how well-defined polymers could be grown via ATRP of oligo(ethylene oxide) methacrylates, from the surface of bovine serum albumin with cleavage initiators attached (that is, grafting from). This could be achieved using either conventional ATRP or AGET in water at 30 °C — conditions that did not denature the protein and yielded polymers with narrow molecular-weight distributions[7]. The reaction temperature, initiator concentration, monomer concentration and selection of the catalytic species were all important factors to achieve success in biologically relevant conditions. The protein–polymer hybrids made in this way are of significant interest to afford materials for enzymatic catalysts and stimuli-responsive systems for biosensors.

Advances in CRP have also created interest in the preparation of polymer conjugates with biological macromolecules for drug-delivery applications. Brent Sumerlin (University of Florida) described the modification of proteins via RAFT using 'grafting from' methods and the careful design of

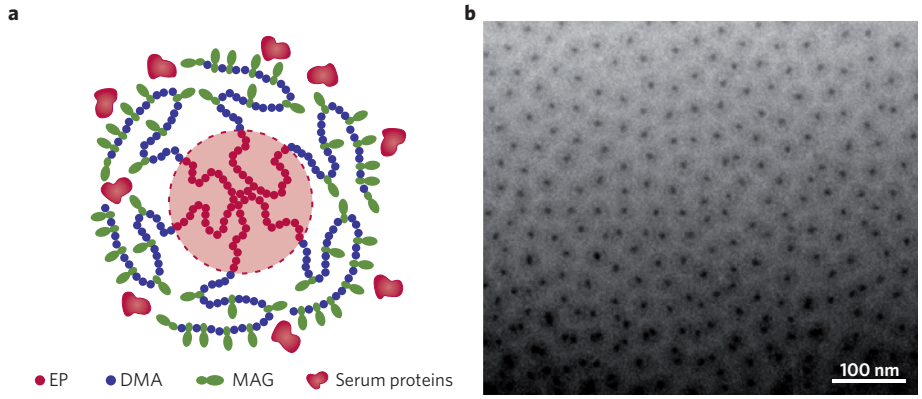


**Figure 2 |** Glucose-functionalized diblock terpolymers. **a**, A schematic representation of the glucose-functionalized diblock terpolymers and the micellar structure formed in fetal bovine serum. The polymer micelles are composed of poly(ethylene-*alt*-propylene)–poly[(*N*,*N*-dimethylacrylamide)-*grad*-(2-methacrylamido glucopyranose)] (PEP–poly(DMA-*grad*-MAG). **b**, A cryogenic transmission electron micrograph of the diblock terpolymer micelles. Image reproduced with permission from ref. 9, © 2012 ACS.

the RAFT transfer agent[8]. First, amine-functionalized lysozymes react with the activated ester functions of trithiocarbonate RAFT transfer agents. Second, poly(*N*-isopropylacrylamide) (PNIPAM) is grafted from the functionalized lysozymes to afford well-defined PNIPAM–lysozyme conjugates with active thiocarbonylthio end groups on the PNIPAM. These reactive end groups can be used for chain extension, thus adding a different polymer, poly(*N*-dimethylacrylamide), to the periphery of the conjugate. The block copolymers could be cleaved from the block copolymer–lysozyme conjugates resulting in the formation of well-defined block copolymers. In the area of drug delivery, the facile preparation of such well-defined polymers and hence, stable polymeric micelles, is critical to create vehicles for the encapsulation and controllable release of small molecule payloads.

Theresa Reineke (University of Minnesota) reported on the preparation of block polymer micelles that married glycopolymers based on methacrylamide modified glucoses and poly(ethylene-*alt*-propylene) copolymer segments (Fig. 2)[9]. These block terpolymers were prepared via anionic and RAFT polymerizations to afford amphiphilic block polymers that formed uniform and well-defined micellar aggregates when dissolved into aqueous media. These polymeric micelles were also observed to be colloidally stable when dispersed in biologically relevant serums. Both dilute solution scattering and cryogenic transmission electron microscopy revealed that the sugar-functionalized polymer corona of the micelle screen suppressed undesirable associations with serum proteins. These types of systems are promising candidates for *in vivo* drug-delivery applications requiring prolonged residence times in the body after injection.

And finally, an elegant example of using CRP to make multifunctional polymeric nanomaterials was described by Karen Wooley (Texas A&M University). These shell-crosslinked knedel-like nanoparticles could be used as vehicles for the delivery of antimicrobial drugs for the treatment of urinary tract infections by conjugation of the nanoparticles with functional adhesion ligands[10].

From the reports above, the field of CRP has evidently matured; however, there are numerous challenges that remain, particularly in the development of complex stimuli-responsive polymers, highly functional polymeric assemblies and nanocomposite materials. These future advances, as well, as other emerging developments in polymer chemistry, will no doubt be featured at the next meeting in Warwick in 2016. ❐

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