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Evolution of macromolecular complexity in drug delivery systems

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Abstract

Designing therapeutics is a process with many challenges. Even if the first hurdle — designing a drug that modulates the action of a particular biological target *in vitro* — is overcome, selective delivery to that target *in vivo* presents a major barrier. Side-effects can, in many cases, result from the need to use higher doses without targeted delivery. However, the established use of macromolecules to encapsulate or conjugate drugs can provide improved delivery, and stands to enable better therapeutic outcomes. In this Review, we discuss how drug delivery approaches have evolved alongside our ability to prepare increasingly complex macromolecular architectures. We examine how this increased complexity has overcome the challenges of drug delivery and discuss its potential for fulfilling unmet needs in nanomedicine.

Nanomaterials have had a key role in delivering drugs, simplifying administration schemes, reducing toxicities and improving disease outcomes. The advancement of nanomedicine (the medical application of nanotechnology) has allowed researchers to evaluate its application in myriad of clinical problems with the goal of developing improved and more efficient therapeutics. In the chemical realm, this includes the integration of multiple functionalities into nanoscaffolds and the development of methods to control the shape and dispersity of macromolecules. In this Review, we highlight how the scope of nanotherapeutics has

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expanded by moving from linear towards architecturally complex branched and hyperbranched structures, and how continued evolution of macromolecular complexity offers opportunities for future applications of nanomedicine.

The need to deliver a pharmacological dose of a drug to a targeted site with high efficacy, using a route that will facilitate patient compliance, is of critical importance for effective and safe disease management[1]. An increase in high-mortality diseases means that there is a growing demand to fill the gap between the arsenal of highly potent active agents in our possession and the significant compromise in quality of life with the traditional treatment options[2,3]. This gap has driven innovation and is fuelling the growth of new technologies for drug delivery — the US market alone is projected to reach several hundred billion dollars by 2021 (REF. 4). Equipping an active pharmaceutical agent with the capacity to overcome physiological obstacles and carry out its function with maximum efficacy comes with considerable design challenges[5,6]. Macromolecular nanocarriers have the potential to revolutionize therapeutics[7], and have provided the scientific community with a platform that has the capacity and potential to evolve with the expanding knowledge and understanding of diseases[8,9]. It can be tailored to different drug delivery mechanisms and can adapt to the challenges accompanying the delivery of therapeutics. Nanomedicine has witnessed substantial growth over the years (FIG. 1), from micelle-based formulations prepared by the polymerization of monomers that are stabilized in solution using surfactants, to smart and innovative technologies that can deliver small to large molecules by conjugation, encapsulation and combinations thereof, through various administration pathways, including intravenous, local, oral, pulmonary, transdermal and transmucosal, and by responding to varied stimuli[10,11]. Considering the rapid development of methods for the synthetic elaboration of macromolecular architectures[12], it is becoming increasingly easy to improve the shortcomings of well-studied technologies and address the emerging need to perform multiple functions using the same scaffold[12,13]. As the parameters of maximum efficacy in drug delivery are better understood[14], a diverse range of macromolecular structures have been developed. Transporting drugs across various biological barriers[15,17] (for example, the skin for topical treatments and the gut-blood barrier for orally dosed drugs) is one of the biggest challenges. Attempts to address this problem has seen the emergence of branched (miktoarm stars) and hyperbranched (dendrimers) macromolecules[18]. Herein, we present a brief overview of material classes used in therapeutic formulations with the intent of providing a roadmap for the development of new clinical materials.

Before developing an understanding of how increasing the macromolecular complexity can improve the delivery of active therapeutic agents, it may be advantageous to briefly review the basic requirements of designing a nanocarrier for systemic delivery[19–21]. First, the nanocarriers should be able to carry a sufficient dose of a hydrophobic or hydrophilic drug and remain in circulation in a physiological medium with tunable leakage. Second, it should target, accumulate and distribute at the desired site in anatomic as well as subcellular compartments. Last, it should be biocompatible. In simplistic terms, a drug delivery vehicle has to solubilize the active pharmaceutical agent, tailor interactions with cells to maximize drug uptake by mechanisms that include, for example, adsorption or endocytosis, and minimize elimination or degradation of its contents before reaching its target. In addition,

the drug delivery vehicle should be non-immunogenic, with a cost-effective synthesis that is easy to scale up.

Drug delivery systems

There has been significant effort devoted to designing efficient nanodevices (for example, liposomes, niosomes and solid-lipid nanoparticles) for delivering pharmaceutical agents. Although not strictly macromolecular carriers, liposomes are some of the most extensively investigated drug delivery vehicles and have seen much success in clinics. It is thus appropriate to briefly discuss their use before the discussion of macromolecular nanocarriers.

Liposomes

Liposomes, formed by the self-assembly of amphiphilic phospholipids, have been explored for drug delivery for more than 50 years[22]. These thermodynamically stable spheres can encage both hydrophilic and hydrophobic drugs, and have become established for their use in clinically approved formulations[23]. Liposomes have offered distinct advantages and considerable promise in delivering a plethora of otherwise inefficient drugs by modifying their physicochemical properties and biodistribution, and by reducing drug toxicities[24]. PEGylation (PEG, poly(ethylene glycol)) is a commonly adopted technique for imparting stealth properties, and PEGylated liposomal nanoparticles have generally been considered to be benign and inert carriers[25]. However, it has been found that PEG itself can elicit an immunogenic response[26]. More recently, anti-PEG antibodies have been described as a new platform that can further enhance the efficacy of liposomal formulations[27,28] by targeting the liposomes towards specific cell types.

There has been immense activity in understanding the main principles of liposomal drug delivery systems and in enhancing their scope and applications by tailoring their preparation method, composition and surface decoration[29]. The collective scientific efforts surrounding liposomal preparations have culminated into several new nanomedicines[30], which are either clinically approved or in clinical trials for the treatment of cancer[26,29] (TABLE 1). In addition, liposomal technology has also been used for fungal and bacterial infections, as well as for gene therapy[27,30].

Despite the wide-spread demonstration of versatility in composition, preparation methods and administration routes, of translocation across several barriers and of success in the clinical translation of liposome-based nanotechnology[31–33], some basic challenges still remain, such as poor understanding of the biological identity of liposomes and difficulties in structural design. The inability to load sufficient cargo in liposomal formulations, combined with leakage, results in only a very small amount reaching the target[34]. The formation of the protein corona at the surface of liposomes (even for those that are PEGylated) can change the drug-release profile of the liposomes *in vivo.* To address these limitations, including fabrication irreproducibility, a different synthetic polymer platform is required. In addition, a careful re-evaluation of the assumed non-cytotoxicity and immunogenicity, as well as the biological fate of phospholipids, is warranted.

Polymers for drug delivery

Natural polymers.—Although the focus of this Review is to evaluate the evolution of structural complexity in synthetic macromolecular nanocarriers, natural polymers have been successfully used in the clinic and are thus worthy of brief mention[35]. Naturally occurring proteins and polysaccharides have been extensively explored as matrix-based nanoparticles for drug delivery owing to their inherent properties, including biocompatibility, degradability and ease of surface modifications[36]. There are several protein-based nanoparticles of interest; however, albumin and gelatin are the two most widely studied systems. Albumin is a versatile protein with high aqueous solubility and stability, multiple binding sites and reactive surface functional groups, which make it an attractive nanocarrier for drug delivery[37]. Abraxane − an albumin-bound nanoparticulate formulation of paclitaxel — is a marketed product in the fight against cancer. It is highly soluble in water and accumulates in tumours using mechanisms that include the enhanced permeation and retention (EPR) effect, as well as the albumin transport pathway[38]. Natural polymer-based nanocarriers offer considerable advantages, and there is much need to expand their scope and develop multitasking nanomaterials. These systems offer great potential that is yet to be explored. With a large pool of data becoming available on new protein-based nanocarriers, more efficient smart nanotechnologies for drug delivery are expected to emerge.

Synthetic polymers.—To facilitate the delivery of a range of small molecules, proteins and nucleic acids, it is essential to be able to engineer the characteristics of polymer-based nanostructures[1,9,11,39]. Tremendous effort has gone into deciphering how supramolecular assemblies of linear amphiphilic polymers and polymer conjugates can be optimized for specificity[40], improved bioavailability, reduced toxicity and desirable pharmacokinetics[41]. Understanding the interplay between composition and surface properties of such polymers, as well as biology, continues to provide impetus for designing new and improved technologies[42–44].

Macromolecule-based drug delivery has come a long way, from humble beginnings using simple and easily accessible materials, to state-of-the-art tailored compositions that take advantage of the diversity of linear, branched and hyperbranched architectures, and hybrids thereof, that are now available[45–54]. The optimization of the overall structure and properties of these polymers has been achieved by chemical innovation. A tremendous amount of effort has gone into the development of efficient methodologies for polymer synthesis, including, for example, living anionic polymerization, controlled free-radical polymerization (atom transfer radical polymerization (ATRP) and reversible additionfragmentation chain transfer (RAFT)), ring-opening polymerization (ROP), and ring opening metathesis polymerization (ROMP)[55–57]. A brief outline of these procedures is provided in FIG. 2. Of the available methods for controlled free-radical polymerization methods, RAFT is becoming increasingly popular in synthesizing amphiphilic block copolymers with narrow poly-dispersities, which could encapsulate chemotherapeutics into their core upon self-assembly. An ABC-type triblock copolymer, poly(ethylene glycol)-*b*-poly(2,4,6-tri-methoxybenzylidene-1,1,1-tris(hydroxymethyl)ethane methacrylate)-*b*-poly(acrylic acid), was prepared by using PEG-cyanopentanoic acid dithionaphthalenoate as the RAFT agent, and by sequential addition of 2,4,6-tri-methoxybenzylidene-1,1,1-tris(hydroxymethyl)ethane

methacrylate and acrylic acid monomers[58]. Upon aqueous self-assembly, the polymeric vesicles were found to be highly efficient in loading and in pH-dependent intracellular release of doxorubicin hydrochloride. A combination of methodologies provides an ideal platform for the synthesis of complex architectures. Sequential ROP of different monomers, or the combination of ROP with controlled radical polymerization, has been used for the synthesis of miktoarm polymers. Ring opening of 2,2-bis(hydroxymethyl)propionic acid coupled to PEG, with an amine functionalized alkoxy amine, followed by sequential ROP of L- and D-lactides, was used for the synthesis of amphiphilic ABC miktoarm polymers[59]. The branched polymers, poly(ethylene glycol)-poly(D-lactide)-poly(L-lactide), contain two complementary polymeric arms that are capable of stereoselective interaction. In an aqueous medium, these miktoarm polymers formed stable micelles with a low critical micelle concentration (CMC), and were highly efficient in the encapsulation and sustained release of paclitaxel. The development of 'click' chemistry, including alkyne-azide cycloaddition, Diels-Alder reaction, thiol-ene addition[60], and other coupling strategies such as thiol-ene Michael addition[61], has further increased the diversity of macromolecular architectures that can be accessed. Alkyne-azide cycloaddition is one of the most extensively explored click reactions for the modification of pre-formed macromolecules as well as their synthesis[62]. Diels-Alder [4+2] cycloaddition has been used to construct a range of macromolecules, and its thermosensitive reversibility has provided a platform to develop degradable nanocarriers for drug delivery[63]. Cycloaddition reactions have also been used extensively to modify small-molecule inhibitors[64,65]. The combination of Huisgen alkyne-azide cycloaddition with reversible Diels-Alder adduct formation between furan and maleimide was used to synthesize dendrimers that underwent retro-Diels-Alder disassembly, and that released a surface-functionalized anti-inflammatory drug (lipoic acid) within the physiological and pathological range of temperatures (37–42 °C)[66]. Thiol-ene coupling is another highly versatile reaction that can be performed under various conditions. It has been used for synthesizing dendrimers in a divergent methodology, starting from a 2,4,6-triallyloxy-1,3,5-triazine core and reacting it with 1-thioglycerol. The solvent-free reaction is initiated with 2,2-dimethoxy-2-phenylacetophenone, and iterative growth is continued by the subsequent generation of terminal alkene moieties on the surface through the addition of 4-pentenoic anhydride; the process is then repeated[67]. Metal catalyst-free methodology is particularly attractive for developing drug delivery nanocarriers. Thiol-ene addition was used to functionalize a PEG-peptide telodendrimer with carboxylic groups for covalent linking of cisplatin[68]. The linear dendritic block copolymer could co-deliver cisplatin with encapsulated paclitaxel with variable concentrations of the combination drugs.

The versatility of the chemical approaches described in FIG. 2 is key in adjusting the self-assembly behaviour of macromolecular materials with the goal of optimizing loading and release characteristics, as well as keeping them intact and in circulation (by modulating the CMC). The diversity of structures made available by simple and scalable synthetic procedures is helping to address the challenge of designing well-defined constructs that incorporate a balanced combination of functions and that can perform predetermined multiple tasks cooperatively and efficiently[69].

Polymeric nanocarriers are being used to address the key issues in drug delivery: loading a sufficient dosage of the active cargo, protecting it from the surrounding environment *in vivo,*

and steadily releasing it at the targeted site without eliciting systemic toxicity (FIG. 3). Many previous studies have focused on characterizing the transport and release mechanisms of these nanocarriers[70,71]. Considering only the polymeric nanoparticle and drug conjugate-based systems, the release is generally guided by diffusion of the encapsulated drug from its reservoir, erosion of the polymeric nanocarrier (or combinations thereof), or degradation of the carrier-drug links. Thus, for polymeric nanocarriers, drug release can be controlled by diffusion, or by activation of the polymer matrix by solvents, local chemistry or external parameters such as pH or temperature[72,73]. The composition and morphology of the polymeric nanocarrier can be expected to majorly influence the release kinetics and pharmacokinetic profile of the drug[74,75].

Colloidal suspensions.—Colloidal nanocarriers that follow a degradation mechanism have been extensively explored for drug delivery. Linear, commercially available polylactide and poly(lactide-*co*-glycolide) (PLGA), which degrade through hydrolysis of ester linkages, are two of the most commonly used synthetic polymers[76,77]. This technology offers potential in controlling the drug release profile and minimizing toxicity owing to the bio-degradability and biocompatibility of the matrix (FIG. 3). Despite advances in the microparticle formulations of these polymers, significant success at the nanoscale has not been achieved. Several new polymers containing functional groups that might follow a similar surface or bulk hydrolysis degradation pathway have been prepared using highly efficient synthetic methodologies, some of which are described in FIG. 2: ROP for poly (caprolactone), poly(anhydrides), poly(phosphazenes), poly(phosphoesters); anionic polymerization for poly (cyanoacrylates); and transesterification of orthoesters with diols for poly(orthoesters). Some issues that have limited the clinical translation of PLGA-based formulations to drug delivery are reproducibility and scalability of polymer synthesis, variability in nanoencapsulation methods, toxicity due to premature and excessive release of therapeutic cargo from nanoparticles, and polymer interactions with the encapsulated drug. New synthetic biodegradable polymers have offered promise in addressing these concerns, and some are at different stages of clinical development[78–83]. Poly(orthoester) IV is one of the members in its family that can be synthesized with reproducible control of its drug release and erosion rates. Injectable formulations of semi-solid poly(orthoe-ster) that were synthesized from a diketene acetal and triethylene glycol or 1,10-decanediol have been evaluated in clinical trials[78]. The synthesis of poly(alkyl cyanoacrylates) has the potential to be scaled up, and BioAlliance Pharma (France) has pursued poly(hexyl cyanoacrylate)-based nanotechnology for doxorubicin (Doxorubicin Transdrug)[84]. The bulk erosion properties of PLGA nanocarriers have been well studied, and the resulting non-toxic products (that is, lactic acid and glycolic acid) can be eliminated by the body's metabolism[85–87]. However, there is much to be understood in terms of the biological fate of the degradation products from the new polymeric systems.

Polymeric micelles

Amphiphilic block copolymers.—Synthetic articulation (that is, the chemical manipulation of separate polymer blocks) in polymer fabrication has led to the development of linear amphiphilic block copolymers. These macromolecules can self-assemble into a range of architectures, including micelles, depending on the medium. Pharmaceutical agents

are often poorly soluble in water; therefore, polymeric micelles with a hydrophobic core can encapsulate drugs efficiently, while presenting a hydrophilic corona to interact with the biological medium. This synthetic polymer platform addresses the key issues noted before for liposomes[86–88]. The choice of hydrophobic blocks (for maximum efficiency in drug solubilization) and hydrophilic blocks (for stealth and enhanced circulation) is made to balance the competing demands of drug loading capacity and controlled/ sustained release at a specific gastrointestinal region for maximum bioavailability with oral delivery[89]. One of the important parameters of micelle formation is the CMC − the concentration beyond which the polymeric chains associate to minimize the free energy ofthe system. CMC is directly related to the stability of the self-assembled structures, and a high CMC will imply disassembly upon dilution in biological fluids[90]. Synthetic advances in controlled radical polymerization methods and click chemistry (FIG. 2) have helped to expand the complexity of available macromolecules and to tailor their selfassembly to more well-defined structures. For example, RAFT polymerization has offered an avenue for developing block copolymers with precisely controlled polymer block lengths that could influence the CMC of the resulting micelles — an important parameter for the stability of drug-loaded nanocarriers[91]. Despite a large collection of amphiphilic block copolymer architectures at the disposal of chemical engineers, much work in drug delivery has been carried out using only amphiphilic diblock (AB) and triblock (ABA) polymers. PEG is the most commonly used hydrophilic block in these systems owing to its high affinity for water and non-toxic nature[88]. Significant success has been achieved in reaching the goal of solubilizing lipophilic drugs using amphiphilic block copolymers. However, important issues related to instability over long periods of time, the short duration of sustained release and poor bioavailability still remain.

Sustained release.—The release of cargo from a polymeric assembly is strongly influenced by the CMC (which determines the overall stability of the structure in the biological medium) and by the strength with which drug molecules are bound in the core. Both are dependent on the amphiphile structure[92]. A lower CMC is desirable for sustained release. One way to achieve this is to increase the hydrophobic content of the copolymer[93], but using new polymeric combinations in diblock (poly(ethylene glycol)-*b*-poly(valerolactone), poly(phos-phazenes)-*b*-poly(*N*-isopropylacrylamide)) and triblock (polylactide-*b*-poly(ethyleneoxide)-*b*-polylactide) copolymers has also sucessfully reduced CMCs[94,95]. For example, the CMC of self-assembled structures obtained from a diblock copolymer that was prepared using ROP of valerolactone initiated by PEG could be fine-tuned by increasing the molecular weight of the poly(valerol-actone) fragment[94]. Slow release of a drug from a micelle can be engineered by increasing the strength of interactions between the drug molecule and the hydrophobic core[83,95]. Micelles obtained from copolymers containing the same hydrophilic blocks (PEG) but different hydrophobic segments of similar chain length, poly (caprolactone) (PEG-*b*-PCL) and poly(L-lactide) (PEG-*b*-PLLA), were shown to have different drug-loading capacity. In one study using the drug quercetin[96], the loading capacity of micelles made from a PEG-*b*-PLLA polymer was found to be higher than that for micelles made from a PEG-*b*-PCL polymer. It was found that the drug interacted most strongly with the PLLA core through hydrophobic interactions, whereas in the PCL-based copolymer, the drug interacted mainly through hydrogen bonding.

Responsive micelles for better bioavailability.—The desire to deliver pharmaceutical agents to the site of action through several different mechanisms and in doses that will maximize efficiency requires manipulation of polymer composition and has led to the development of 'smart polymers' (REF 97). These macromolecules can sense biological environmental changes and respond to various physical and chemical stimuli — including, for example, pH, temperature, ultrasound and ionic strength — by altering their physicochemical proper-ties[98,99]. Systems that can respond to changes in pH offer opportunities to maximize absorption at a defined point along the gastrointestinal tract, or at inflamed and cancerous tissue where the physiological pH is known to differ from surrounding tissue. Numerous copolymers that incorporate a pH-responsive block, and thus enhance the bioavailability of drugs through this mechanism, have been synthesized. For example, using PEG as a hydrophilic macroinitiator, block copolymers containing variable lengths of hydrophobic fragments, poly(ethylene glycol)-*b*-poly(alkyl acrylate-co-methacrylic acid) were prepared using ATRP. The presence of pendant COOH groups in these polymers led to pH-dependent aggregation, and their critical aggregation behaviour was found to be tunable by varying the hydrophobic chain length[100]. Drug release from these aqueous assemblies could also be controlled by pH, and increased upon the change from highly acidic to basic medium. This strategy of using pendant acidic groups to produce pH-responsive polymers has been extensively used for controlled release of encapsulated cargo. For example, micelles that could respond to pH changes along the gastrointestinal tract were synthesized by copolymerization of acrylic acid with poly(ethylene glycol)-*b*-(4-(2-vinylbenzyloxy) -*N,N*-(diethylnicotinamide))[101], and a multifunctional micelle system with varied pH sensitivity under different environments was prepared from a mixture of two block copolymers, poly(L-histidine)-*b*-poly(ethylene glycol) and poly(L-lactide)-*b*-poly(ethylene glyclol)-*b*-polyhistidine[102]. Poloxamers are block copolymers containing a hydrophobic central segment, end capped with hydrophilic blocks. The self-assembly behaviour of such block copolymers containing PEG and poly (propylene oxide) in an ABA composition is temperature sensitive. The CMC, which decreases with temperature, and thermoreversible aggregation (gelation) of these assemblies have been utilized for the controlled release of drug cargo[103]. Block copolymers ofpoly(*N*-iso-propylacrylamide) and PEG, and polylactide-*b*-poly (ethylene glycol)-*b*-polylactide have also been widely studied as thermoresponsive systems[104]. Micelle formulations based on thermosensitive polymers, such as non-ionic pluronics (for example, SP1049C developed by Supratek Pharma for the delivery of doxorubicin) have shown great promise in clinical trials for the treatment of gastric and oesophageal cancer[105]. Poly (*N*-isopropylacrylamide) (PNIPAM) has a low cloud point (32 °C) and is insoluble at body temperature in an aqueous medium. In block copolymers containing hydrophilic PEG, this temperature-dependent solubility allows the facile preparation of micelles, which could deliver their cargo at the cancerous site using local hypothermia[106]. In general, for *in vivo* applications, the lower critical solution temperature (LCST) of PNIPAM needs to be raised to avoid aggregation of micelle formulations upon administration. Much effort has been devoted recently to fine-tune the LCST of PNIPAM by introducing hydrophilic segments in its block copolymers. Using free-radical copolymerization of *N*-isopropyl amide and acrylamide, followed by tin-catalysed ROP of lactide, the block copolymer poly(*N*-isopropylacrylamide-fo-poly(acrylamide)-fo-poly(D,L-lactide) had an LCST of 41°C (REF 107). The docetaxel-loaded micelles were

thermosensitive, and the drug release could be triggered by hyperthermia. Similar strategies of adjusting the LCST by copolymerization with hydrophilic monomers have been used to prepare block copolymers poly(*N*-isoprpylacrylamide-*N*-hydroxymethylamide)-fo-poly(methyl methacrylate) (LCST 42.8 °C)[108], and poly(*N*-isopropylacrylamide-*N,N*-dimethylacrylamide)-fo-poly(caprolactone) (40 °C)[109]. Advances in synthetic methodologies have made it possible to tailor triggering parameters, such as pH and temperature, in polymeric assemblies. Only through more systems getting to clinical evaluations can such adjustments be assessed for reaching the peak of their efficacy.

Polymer-drug conjugates.—Chemically linking the drug to a polymer can influence its stability, solubility and bioavailability, and this concept has been extensively explored[110]. With the guidance provided by the work of Ringsdorf[111], and the other research that followed, it was suggested that polymer-drug conjugates can help to address several of the key issues facing drug delivery, including long blood circulation times, targeting, accumulation and retention (FIG. 3). The concept of solubilizing the drug by chemically linking it to a macromolecule has been widely applied[112,113], with PEGylation being the most commonly used method. Several such conjugates have successfully made it into the clinic or are currently under clinical evaluation (TABLE 1). Progress in this area is dominated by, and will continue to be made, using synthetic evolution[114] — especially in linker methodologies, for example, click chemistry[115,116] (FIG. 2). It is expected that the development of new conjugates that exploit our increasing knowledge of biology at disease sites can help to advance the field[117].

Clinical translation

Since the inception of the field of nanomedicine, there has been an expectation that parallel advances in disease understanding and nanocarrier engineering would lead to rapid progress in the development — both preclinical and clinical — of nanoparticle-based drug formulations[118]. Clinical translation is a complex and time-intensive process, and a recent review article highlights these challenges[119]. An overview of nanoparticle-based drug delivery vehicles that have been commercialized, as well as candidates that have demonstrated promise in clinical trials, shows that these are dominated by liposomal formulations[119–121] (TABLE 1). Polymers have offered synthetic versatility, tunability, adaptability and have been explored for a very long time. Their modest bench-to-bedside translation can be criticized, but the cautious approach towards their use must also be commended. One of the main challenges today is that when systems fail, we rarely know why. The use of new polymers in nanomedicine requires a detailed investigation of their toxicity. In general, the interaction of nanoparticles with biological systems in the human body has not been fully explored and is currently poorly understood. We believe that a deeper understanding of the biological identity of nanoparticles is needed for more predictive clinical translation[122]. The evolution of available synthetic methods has produced a diverse library of these macromolecules; however, only a handful of these have been intensely investigated and ultimately approved for use. For example, polymer-drug/antibody/protein conjugates may be easily accessible with advances made by chemists and

may perform admirably in laboratory settings. However, even when an already approved pharmaceutical is modified in this way, a further lengthy testing protocol is required.

The slow progress to clinical trials can be difficult to evaluate. It is entirely expected that a higher burden of proof is placed on formulations to be used in the clinic. It is clear that scaling up synthesis to the quantities needed with quality controls and batch-to-batch reproducibility, while obtaining detailed toxicity and safety profiles, are just the basic requirements. Nanocarriers need to cross several complex biological barriers and reach the target site. Addressing these challenges with a detailed evaluation is crucial for the successful clinical translation of any drug delivery vehicle[123]. In addition, the small-animal model studies that are used as clinical benchmarks may be of limited scope, and effects may not be reproduced in human patients because of far more individual complexity and disease diversity. Future studies may need to be evaluated on a broader animal platform.

Polymers have evolved synthetically, but their versatility is evaluated by chemical engineers, who consider how the strengths and failures of each can guide the successful implementation of these polymers into technology in the future[124,125]. Imaging at the single cell level has had an important role in deciphering how nanomaterials work and fail *in vivo*[126]. As the biological mechanisms of debilitating diseases, su ch as cancer, become better understood, the arsenal of available polymer structures will need to increase further to match our expectations.

Emerging macromolecular complexity

The limited clinical translation of polymeric systems that have proved successful *in vitro* has engaged chemists, biologists and engineers in determining the key issues that lead to lower efficacy *in vivo*[127]. Significant effort is being made to fully explore the roles of nanostructure assembly, morphology, surface characteristics, mode of delivery and intracellular accumulation[128,129]. For their part, chemists have developed synthetic routes to more elaborate and adaptable structures that could provide further flexibility in engineering smart nanomaterials[130].

Studying the variety of linear macromolecules used in polymer therapeutics, it is increasingly clear that their compositions must be carefully assessed to tune their efficacy as drug carriers. The molecular weight and overall shape can significantly influence their biological interactions and cellular uptake mechanisms. New platforms with variable self-assembly characteristics, enhanced drug-loading capacity, plasma stability, and which can incorporate desirable traits such as multivalent surfaces or homogeneity, may offer promise for new delivery vehicles[131]. This can be achieved by the evolution of polymer structure from linear to branched and hyperbranched architectures with unique and tailored physical and biomedical properties[132,133]. The latest developments in synthetic methodologies have resulted in the production of nanocarriers for drug and gene delivery, and in the introduction of multiple functions into a single scaffold[52,134].

Branched polymer nanotechnology

The application of branched and hyperbranched polymer structures in drug formulations, relative to their linear counterparts, remains in its infancy[135]. These polymer architectures offer the potential to tailor the dispersity and functionalization of structural compositions, and to introduce multifunctional character using orthogonal chemistries[136]. With rapid progress in synthesis for easy access and large-scale production[137], there exist clear opportunities for such structurally flexible macromolecules in addressing key issues related to drug delivery and theranostics.

Miktoarm polymers

The lessons learnt while studying polymeric micelles suggest that there are still some basic issues related to the efficiency of drug incorporation, stability (disassembly) of the nanocarrier while travelling in a biological medium and its release at a specific site. These may be addressed by designing new carriers in which the chemical structure of the polymers and hydrophobic core, and the CMC of the resulting micelles, can be tailored. Branched architectures, such as miktoarm polymers, constitute one such example of macromolecules, in which a number of polymeric arms with different (desired) chemical compositions, molecular weights or functions, are tethered to the core, resulting in unique physicochemical properties. These polymers have been prepared using similar methodologies that have been widely explored in the synthesis of linear block copolymers[138–140] (FIG. 2). Owing to their shape and programmable amphiphilic architecture, a range of self-assemblies of structural diversity and complexity, including micelles, compartmentalized micelles and vesicles (polymersomes), have been fabricated[139–144] (FIG. 4). Although a relatively new area of research, synthetic evolution has made such structures accessible for detailed investigation. It is clear that self-assemblies from miktoarm polymers have narrow size distributions and lower CMCs, which could translate into higher stability in physiological medium, and better loading efficiencies and release characteristics[145,146].

Because it is the branched architecture that is being evaluated in developing more efficient nanoformulations, using polymeric arms that are composed of US Food and Drug Administration (FDA)-approved materials may help to expedite their clinical implementation. Miktoarm polymers that are being explored for drug delivery often incorporate such FDA-approved or biocompatible polymers, including PEG, PCL and polylactides, into their arms. Such amphiphilic AB_2- or ABC-type architectures have been synthesized from a core on which sequential coupling of PEG arms of predetermined molecular weights, using copper catalysed alkyne-azide click chemistry, is followed by ROP of caprolactone (FIG. 5a). These miktoarm polymers have shown promise in enhancing solubility and drug loading efficiencies of lipophilic drugs, such as nimodipine and curcurmin[147,148], and in targeting specific cell organelles[149]. These interesting properties of branched macromolecules have been further extended with synthetic elaboration into stimuli- responsive systems. $A_3B_3C_3$-type miktoarm star polymers were synthesized using a combination of ROP and activators regenerated by electron transfer atom transfer radical polymerization (ARGET ATRP)[150] (FIG. 5b). Selfassembled micelles from these pH-responsive miktoarm polymers could incorporate sufficient quantities of doxorubicin and

were shown to change the morphology upon variations in pH, which led to an enhancement of the rate of doxorubicin delivery[150].

Using articulation of the available synthetic methodologies, the composition of miktoarm stars could be varied to develop multiple stimuli-responsive branched copolymers[151,152] (FIG. 6). The flexibility in the fabrication of miktoarm polymers may also offer opportunities to combine polymer-drug conjugation with encapsulation, yielding smart nanoassemblies for multiple drug therapy[153].

Dendrimers

Detailed studies of therapeutics that use linear polymers have highlighted several common problems. Structural heterogeneities that arise from self-assembly result in differences in drug loading, and there is limited scope for drug conjugation and for introducing multiple functionalities. Dendrimers — constructed using controlled divergent and convergent reaction sequences — yield globular, well-defined, hyperbranched, monodisperse and multivalent architectures[154]; thus, they provide a new platform to address these issues[155]. In addition, dendrimers may offer enhanced permeation across barriers for better drug distribution because of their shape and multivalent surface[156]. Since the very first reports of poly(amidoamine) (PAMAM) dendrimers, a large range of synthetic methodologies have been developed, which have provided access to a plethora of backbones with any desired number of generations. In drug delivery, PAMAM dendrimers stand out as one of the most extensively explored dendrimers for applications in biology and are commercially available[157].

The dendrimer architecture offers the potential for these systems to be used as unimolecular micelles for the encapsulation of drugs[158]. In addition, their multivalency can be exploited in dendrimer-drug conjugates by surface modification[159]. Considering the stability of unimolecular micelles at varying concentrations, dendrimers were initially considered an alternative to polymeric micelles, and several studies looked at encapsulating various drugs into the internal cavities of dendrimers[160–162]. However, difficulties with drug release, improved performance of micelles prepared from linear and branched polymers, and higher costs made these systems unattractive for further evaluation and translation into drug delivery technology.

Covalent linking of drugs to dendrimers is an area that has been well developed considering: the availability of various synthetic methodologies (including the chemical reactions and coupling methodologies described in FIG. 2) for dendrimer synthesis, as well as surface and internal functionalization; multivalency tailored to specific needs with generation number; and the possibility of controlled release using degradable linkers with drugs[163,164]. Much of the work in dendrimer-drug conjugation has been done on commercially available PAMAM dendrimers using a statistical approach to functionalizing the periphery of different generation dendrimers. This strategy has significant issues related to irreproducibility and heterogeneity in the formulation, which once again has hindered translation of this technology into clinical trials. The challenge as with drug encapsulation into dendrimers is one for chemists, and there have been several advances in the field in which new backbones and better linker chemistries have been developed[165–168].

One area in which the traits of dendrimers might be more fully exploited is in the introduction of multiple functionalities for targeting, imaging and stealth. There are opportunities for chemists to expand the synthetic complexity of dendrimers using high-yield reactions[166,167], such that they have a controlled spatial distribution of different functionalities at their surface. Combination therapies may also be improved by the ability to deliver a precise ratio of two different agents using the same scaffold. Higher generation dendrimers have been widely explored for introducing multiple functions on their surfaces. With the detailed analysis of dendrimer-based drug delivery, it is becoming clear that there may be issues related to homogeneity of higher generation dendrimers and to the statistical distribution of surface-bound moieties in post-functionalization methods, which lead to irreproducible pharmacokinetics. However, lower generations with well-defined and reproducible synthesis may be more useful for technological advances. New synthetic methodologies based on orthogonality of functional groups are beginning to emerge for the preparation of bi- and tri-functional dendrimers, which have shown promise in studies carried out both *in vitro* and *in vivo*[168–172].

Several products based on dendrimers have been marketed[18], including Ocuseal, SuperFect, Alert Ticket and Stratus CS. Examples of clinical translation of dendrimer- based nanotechnology are also beginning to emerge. For example, Vivagel, a polyanionic dendrimer-based topical microbicide developed by Starpharma, is currently in phase III trials for the treatment and prevention of bacterial vaginosis. Starpharma has also developed a dendrimer-based drug delivery system, DEP, for the anticancer drug docetaxel, which is in phase I clinical trials. The potential of dendrimers has not been fully exploited yet, and as the synthetic challenges facing dendrimer structure build-up and subsequent functionalizations are addressed, it is hoped that more products will enter clinical evaluations.

Telodendrimers

Linear, branched and hyperbranched macromolecu- lar architectures have offered distinct properties, which have been individually well explored for applications in biology. Attempts have also been made to address their limitations within their own space. However, the solution may lie in developing hybrid macromolecular architectures that could combine their useful traits and offer opportunities to collectively address challenges in drug delivery to advance the field at a fast pace. Architectural copolymers, also referred to as telodendrimers, are such macromolecules, in which the ease of synthesis and the self-assembly of linear polymers are coupled with the uniformity and multivalency of dendrimers[173] (FIG. 7). The driving force for interest in telodendrimers for biological applications is the synthetic ability to tailor their chemical composition, molecular weight and number of generations of the hyperbranched block, and to control the morphology of the self-assemblies that result and their stability. Because the synthetic methodologies for constructing linear and dendrimer blocks of these copolymers are well established (FIG. 2), the evolution in architectural complexity oftelodendrimers has directly arisen from the ability to stitch dendrimer fragments together in a predictable and reproducible manner — that is, the development of click chemistry[174]. The entry of these architectural copolymers into the field of drug delivery is relatively new[175]. There have been some interesting studies that have explored

the role of the morphology of linear-dendrimer block copolymers on the micelle assemblies and the effect that the latter has on drug encapsulation, circulation times and cellular uptake of the nanocarriers[176–178]. The scope of these hybrid materials can be expanded further by, for example, making them respond to external stimuli, including pH and temperature. Such smart hybrid materials will be of interest because the response could be triggered through changes in either block[179]. Much remains to be done in terms of understanding and exploiting the potential of these promising materials, and progress will come, once again, from synthetic expansion in laboratories, as well as recently explored computational design and combinatorial chemistry[180].

Macromolecules as therapeutics

Advances in understanding the interactions of polymers themselves with biological systems have given rise to increasing interest in developing novel methodologies to cure diseases. This has led to the emergence of a field commonly referred to as macromolecular therapeutics[181,182]. These macromolecules, which do not carry any encapsulated or covalently linked pharmaceutical agent, offer a new direction in combating ever-evolving pathologies[183]. Drug-free macromolecules in various shapes and sizes have demonstrated therapeutic efficiencies and have been suggested to be of particular value, because they do not carry pharmaceutical agents that could themselves invoke immune response and systemic toxicity. In some of the earlier studies, water soluble and long circulating *N*-(2-hydroxypropyl) methacrylamide copolymers with grafted biorecognition motifs were shown to induce programmed cell death[184]. Macromolecules containing carefully designed structural motifs bind to non-internalized or slowly internalizing receptors on the cell surface and cause receptor coupling or clustering, leading to cell death[185] (FIG. 8). The cell-surface biorecognition principles that are responsible for apoptosis and information from biological mechanisms offer potential and guidelines for designing novel macromolecular therapeutics that target specific diseases.

Hyperbranched drug-free PAMAM generation 4 and 5 dendrimers containing amine, hydroxyl and carboxylic acid surface groups have been shown to possess anti-inflammatory properties, which in some cases has been higher than the drug indomethacin. It was hypothesized that the origins of anti-inflammatory effects may be related to the inhibition of cyclooxygenase (COX-2) activity; however, a detailed evaluation of the specific mechanism(s) is needed to help establish structure-property relationships in these dendrimers[186]. Much smaller dendrimers (generation 1) synthesized using alkyne-azide click chemistry, containing hydroxyl terminal groups and no (other) active pharmaceutical agent, were shown to have concentration-dependent anti-inflammatory behaviour[187]. An evaluation using computer-assisted molecular docking simulations, performed using molecular operating environment software, has suggested that the mechanism of action may involve dendrimer interaction with inducible nitric oxide synthase (iNOS) and COX-2 enzymes, with reduction in nitric oxide release and inhibition of prostaglandin synthesis. Anti-inflammatory activity was found to be dependent on dendrimer size and terminal functional groups, and lower generation hydroxyl terminated dendrimers were found to have a better fit to the enzyme binding active site, inhibiting their activity (FIG. 9). Micelles assembled from branched A_2B miktoarm polymers containing PEG and PCL arms, and that

are absent of any encapsulated drug, have also been shown to reduce nitric oxide release at a level comparable with that of the drug-loaded (nimodipine) micelles[146]. It is anticipated that the scope of macromolecules as therapeutics will be further expanded by more detailed evaluations of the mechanisms by which naked nanocarriers provide a pathway for biological interference.

Several elegant studies have explored designing polymer-based nanoparticles that could emulate aptamers and antibodies in interacting with biomacromolecules to cloister toxins[188–190]. Considering the diversity of macro-molecular architectures that is currently at our disposal and that can be easily synthetically tailored, this approach offers enormous potential in fine-tuning binding capabilities for a range of biomedical applications. The area of macromolecules as therapeutics is still in its infancy, and a detailed understanding of this platform may provide novel pathways to engineer new technologies.

Accelerate clinical validation by matchmaking

Macromolecular nanoparticles have had a key role in delivering drugs, simplifying administration schemes, reducing toxicities and improving disease outcomes. Several new platforms have been developed in which the structural dispersity of macromolecules has evolved. This enormous scientific investment has been made with the intention of inventing better and more efficient therapeutic interventions for diseases such as cancer. However, clinical evaluation of nanotechnology suggests that patients suffering from the same cancer type respond differently to a nanoparticle-based drug formulation. One of the common methods to deliver drug-loaded nanoparticles to the tumour site relies on the EPR effect. A heterogeneous response to nanoparticle therapy could thus be related to variability in the EPR effect in the tumour tissue of the same cancer type in different individuals. This suggests that the design of macromolecular nanoparticle cancer therapeutics needs to be strongly influenced by tumour structural features and local biology[191]. The solution to this problem may lie in a shift towards personalized medicine and by investing in understanding the properties of tumours in a particular set of patients. Imaging tools continue to aid in expanding our knowledge ofthese local facets[192]. To facilitate clinical efficiency of nanoparticles and significantly improve quality oflife in cancer patients, individual EPR effects may need to be evaluated in patients first by, for example, using imaging-enabled nanoparticles before matching the effect with the drug payload[193]. In a recent study, such a protocol was demonstrated in which fluorescently labelled Fe_2O_3 magnetic particles were used to predict co-localization of therapeutic nanoparticles constructed from block copolymers, poly(D,L- lactic-co-glycolic acid)-*b*-poly(ethylene glycol)[193]. Such a novel platform offers significant potential[194] and can evolve with polymer complexity to accelerate clinical validation of nanoparticle technology[1,2,29,116,121,157,195].

Conclusions

Significant progress in engineering polymer-based nanocarriers has been made as a result of the converging efforts from different scientific disciplines. Biologists and pharmacologists continue to provide an understanding of the biological mechanisms involved in different diseases. This offers scientists a platform to develop nanotechnology to deliver active

pharmaceutical agents efficiently to desired sites. Chemistry has a crucial role in equipping them with tools for the relevant nanotechnology, and macromolecules are key components in this regard. A complete picture has not yet emerged, but it is clear that the size, shape, functional groups and overall morphology of the nanocarriers are crucial parameters for their efficacy in drug delivery. Design of macromolecular nanoparticles through a detailed understanding of these parameters will help the invention of better and more efficient therapeutic interventions, as well as facilitate the process to expeditious clinical translations. Miktoarm polymers are relatively new and the scientific community has begun to evaluate their efficacy as nanocarriers in detail. It will be necessary to carry out a detailed comparative analysis of these branched systems with block copolymers to develop better macromolecule-based nanotechnologies for drug delivery. Dendrimers have been well studied, although efforts have concentrated on PAMAM-based dendrimers — perhaps justifiably so given their commercial availability. New backbones are now appearing on the market, and it is hoped that any shortcomings noted earlier, for example, homogeneity of higher generation dendrimers and the statistical distribution of surface-bound moieties in post-functionalization methods leading to irreproduc-ible pharmacokinetics, will be addressed to expedite their entry into clinical translations. Advances in drug delivery will be made by the synthetic adaptation of polymer complexity that has been made available and interfacing it with biology. The scientific community understands the need to direct unique and advantageous characteristics of each macromolecule to address specific unmet needs of a desired pathology. Rapid advances in clinical evaluations and a move towards personalized medicine will arise from a better understanding of the successes and failures of macromolecule-based drug delivery technologies. Ultimately, this will spur chemists to improve on their designs for macromolecular nanocarriers, and continued collaboration among multidisciplinary teams will subsequently help expedite realization of their potential.

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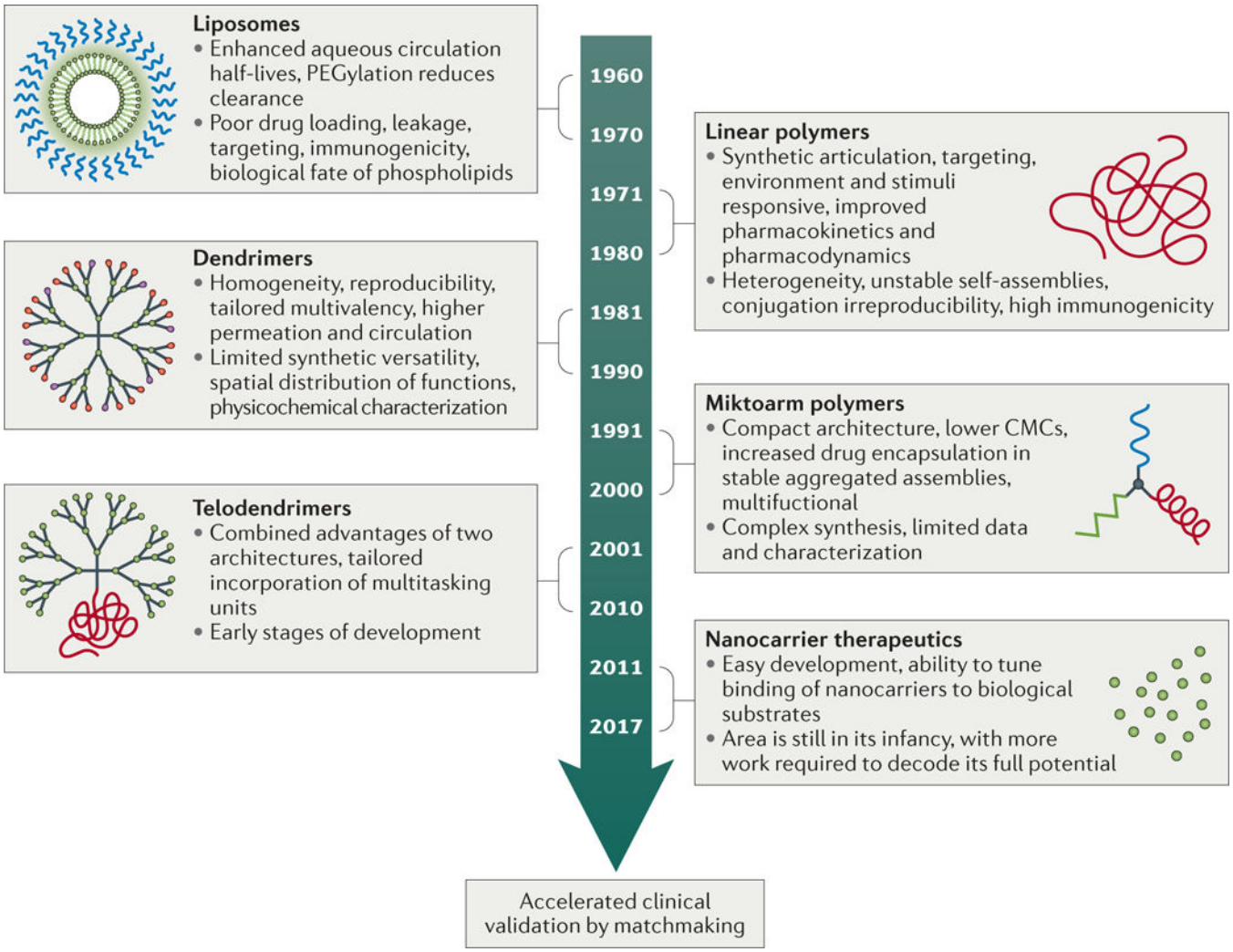

Figure 1 |. Analysis of macromolecular structure evolution in drug delivery.

Nanomaterials have had a keyrole in delivering active pharmaceutical agents to the diseased site. Here, we provide a brief summary of the timeline, advantages and disadvantages of each category of nanocarriers, ranging from early discoveries of phospholipids and linear polymers to branched and hyperbranched macromolecules, hybrids thereof, drug-free macromolecules as therapeutics themselves, and strategies to accelerate bench-to-bedside transition. CMC, critical micelle concentration; PEG, poly(ethylene glycol).

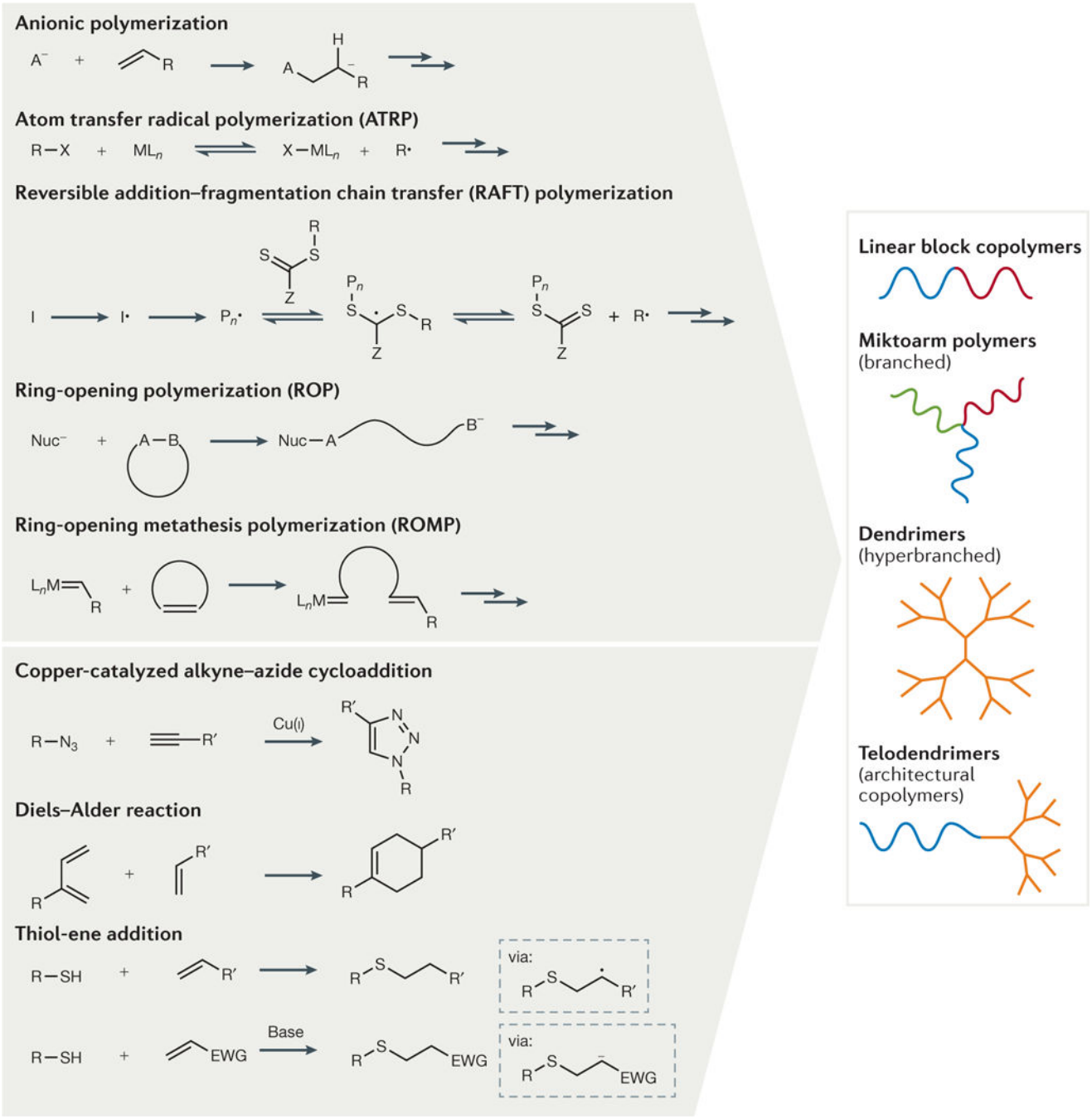

Figure 2 |. Macromolecular architectures in drug delivery and examples of the methodologies for their synthesis.

Some of the common synthetic methods (upper left panel), and chemical reactions and coupling strategies (lower left panel) that have been used for the synthesis of linear, branched and hyperbranched macromolecules and hybrids thereof (right panel) are shown. EWG, electron-withdrawing group; L, ligand; M, transition metal; Nuc^-, nucleophile.

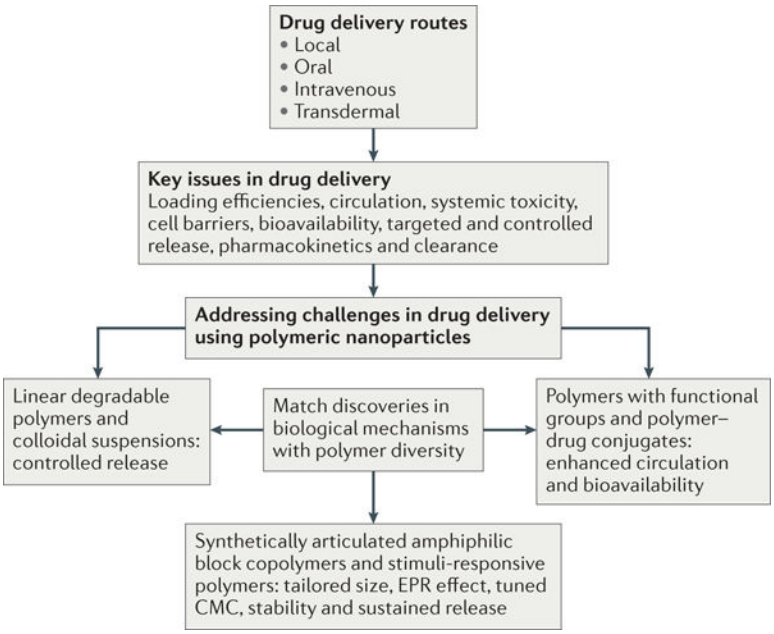

Figure 3 |. Common drug delivery methods: oral, intravenous, transderm alandlocal administration.

The challenges that we face in our efficacy in treating a particular disease can be resolved by using our understanding of the local biology in designing a suitable macromolecule-based nanocarrier for drug delivery. Advances in synthetic methodologies have allowed the design of linear polymers that can increase blood circulation, bioavailability, active and passive (via the enhanced permeability and retention (EPR) effect) targeting, controlled release, and that can respond to various external stimuli. The CMC refers to the critical micelle concentration of polymeric assemblies from amphiphilic polymers, and it is an important parameter that determines the in vivo stability of drug-loaded micelles.

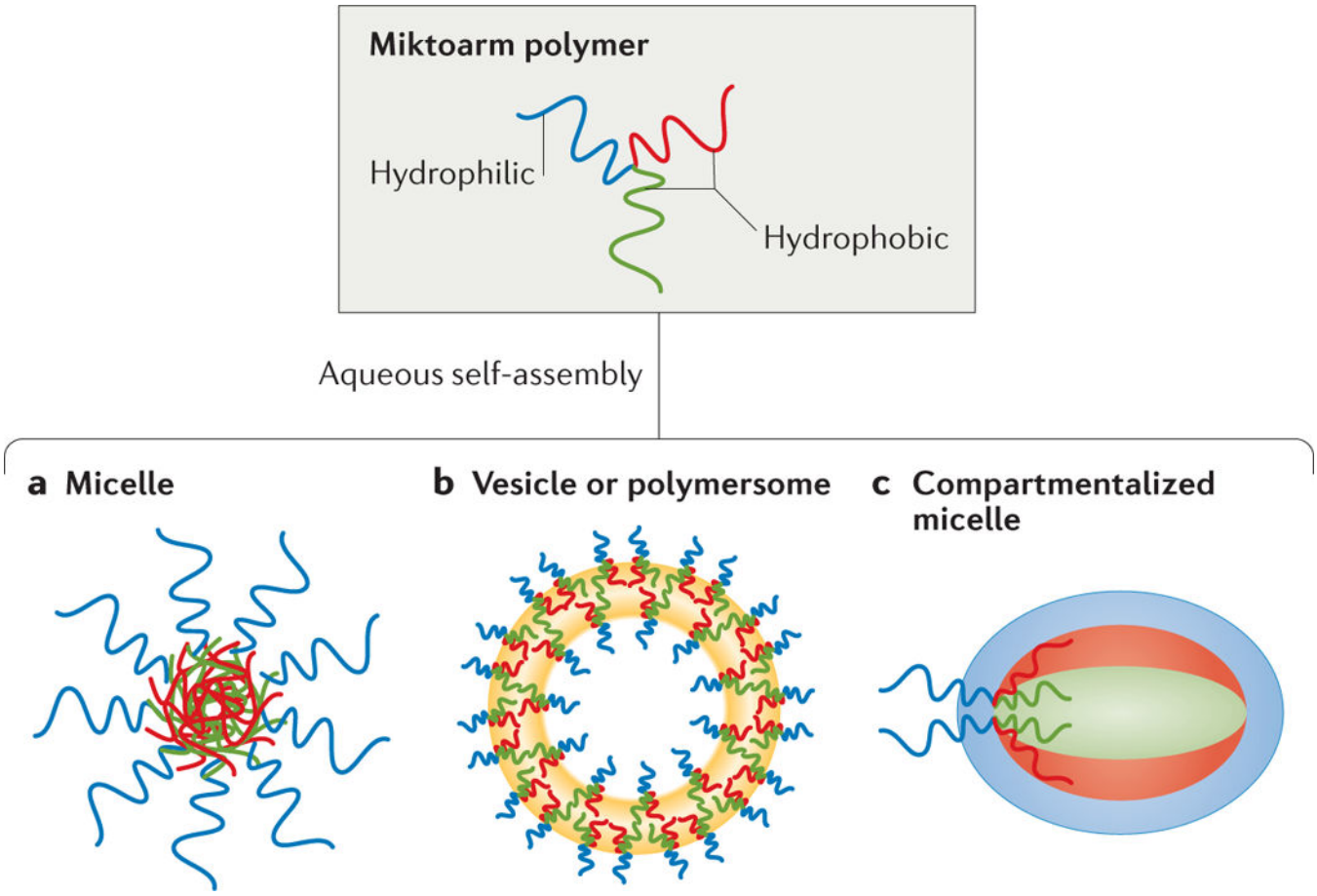

Figure 4 |. Self-assembled structures from an ABC-type amphiphilic miktoarm polymer.
In this ABC-type amphiphilic miktoarm polymer, A is hydrophilic, and the B and C arms have variable hydrophobicity. **a** | Mitkoarm polymers can form spherical aggregates, known as micelles. **b** | Mitkoarm polymers can also form vesicles (hollow spheres) or polymersomes (polymer-based liposomes). **c** | A compartmentalized micelle −a spherical aggregate in which each arm of the miktoarm polymer leads to its own hydrophilic and hydrophobic regions — can also be assembled.

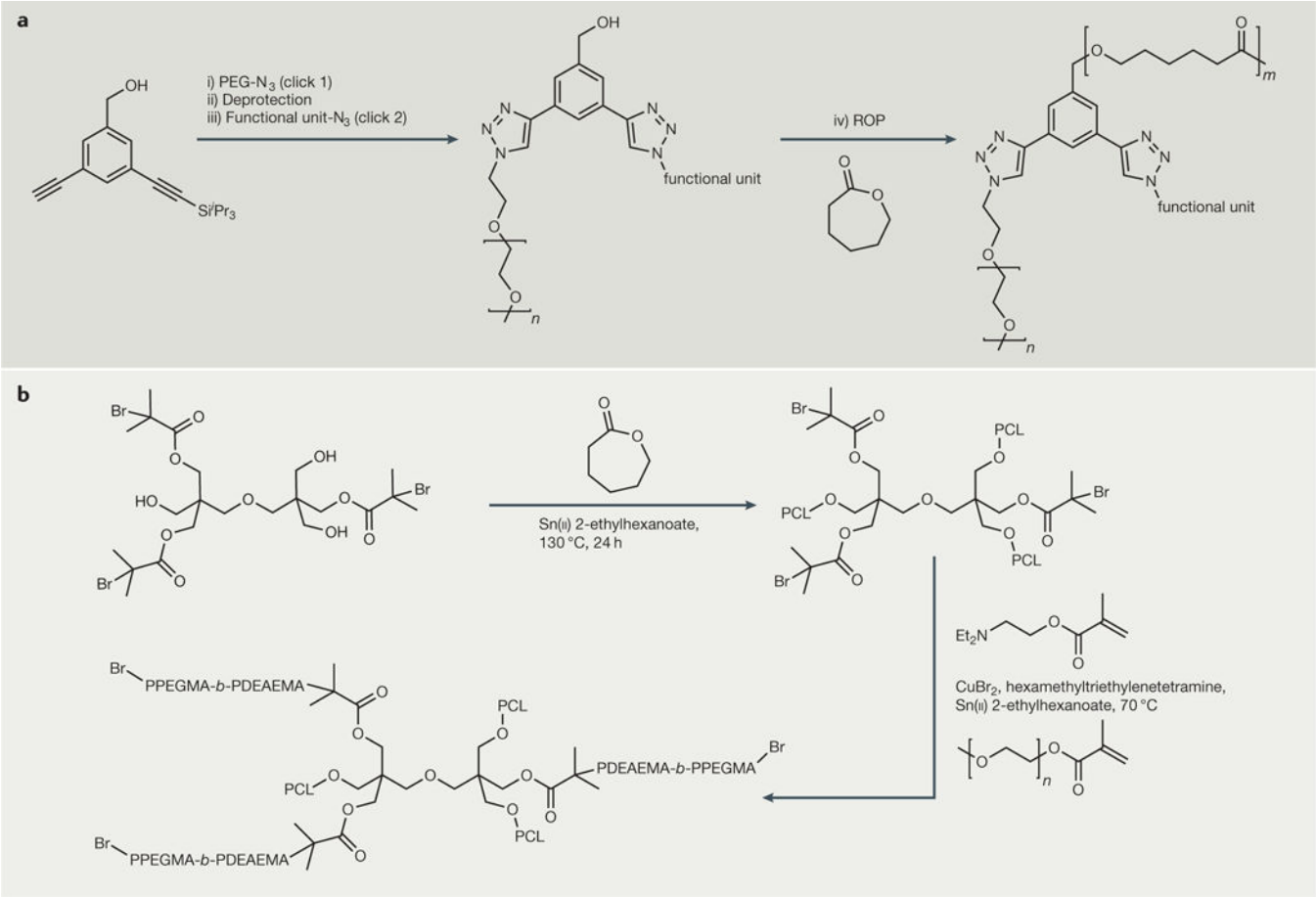

Figure 5 |. Synthesis of architecturally complex branched macromolecular structures.
a | Synthesis of mikto arm polymers using combined copper-catalysed click and ring-opening polymerization (ROP) reactions. The core with three orthogonal functional groups (3-(triisopropylsilylethynyl)-5-ethynylbenzyl alcohol) was prepared from 3-bromo-5-iodobenzyl alcohol by sequential Sonogoshira coupling of triisopropylsilylacetylene and trimethylsilylacetyl- ene: (i) click 1 with PEG-N_3, $CuSO_4$-$5H_2O$/sodium ascorbate, H_2O/tetrahydrofuran (THF), room temperature, overnight; (ii) tetrabutylammoniumfluoride/THF, overnight; iii) click 2 with another functional entity with an azide group, $CuSO_4$-$5H_2O$/sodium ascorbate, H_2O/THF/dimethylformamide, room temperature, overnight; iv) toluene, Sn(ii) 2-ethylhexanoate, reflux, 24 h. **b** | Synthesis of A_3B_3 miktoarm polymer using ROP and continuous activators regenerated by electron transfer atom transfer radical polymerization (ARGET ATRP). The difunctional initiator, prepared from dipentaerythritol and 2-bromoisobutyryl bromide, was used to carry out sequential ROP of caprolactone. This was followed by continuous ARGET ATRP of 2-(diethylamino)ethyl methacrylate (DEAEMA) and poly(ethylene glycol) methyl ether methacrylate (PEGMA) in sequence to yield the miktoarm polymer. PCL, poly(caprolactone).

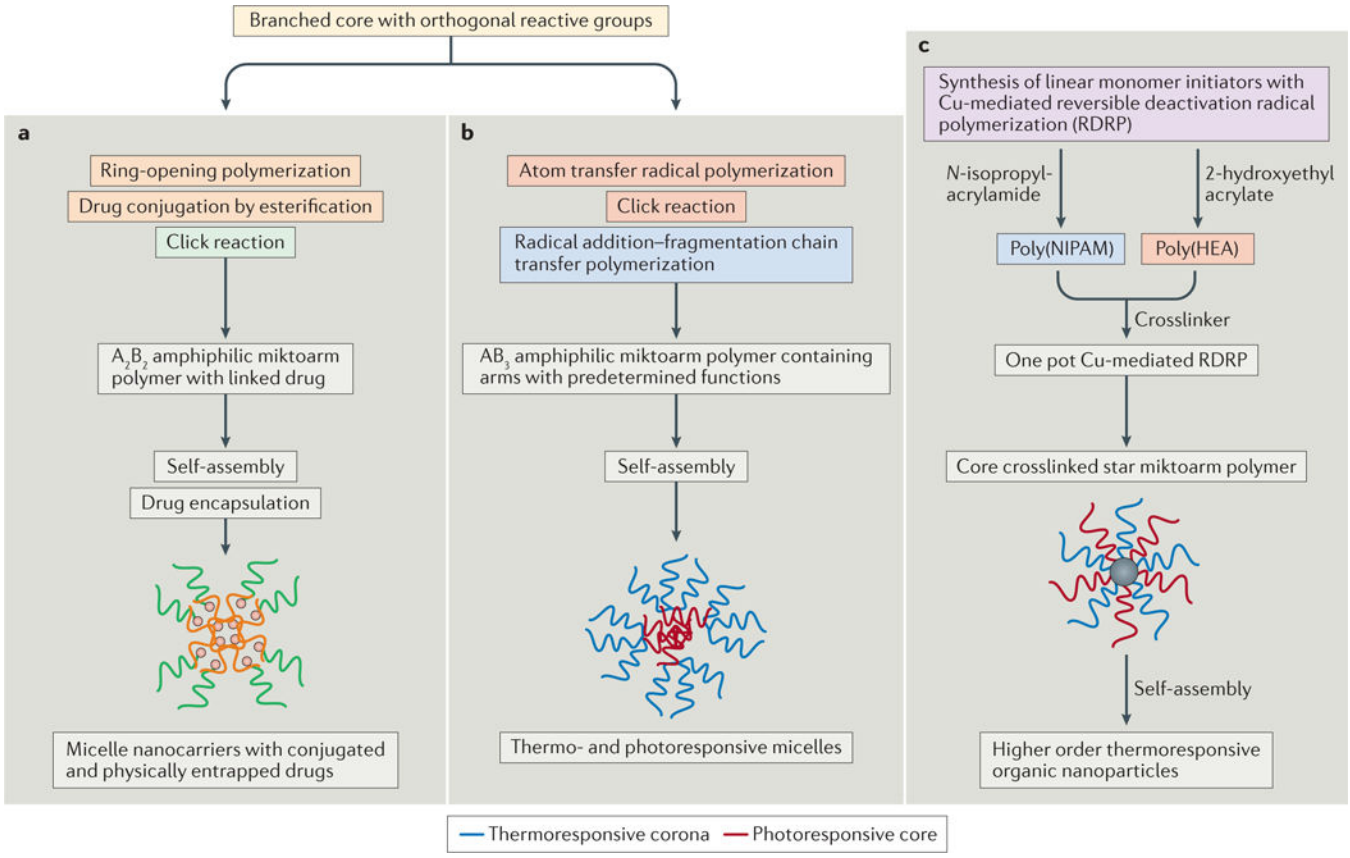

Figure 6 |. Examples of smart nanoassemblies constructed using a combination of differentsynthetic methodologies.

a | Starting with 2,2-bis(bromomethyl)propane-1,3-diol, and carrying out sequential reactions — i) ring-opening polymerization of caprolactone, ii) azidation of bromides at the core, iii) esterification to covalently link ibuprofen, iv) Cu-catalysed click reaction of alkyne-terminated poly(ethylene glycol) — led to the formation of an amphiphilic A_2B_2 miktoarm polymer with conjugated ibuprofen. This drug-conjugated polymer formed spherical micelles upon self-assembly in water, which showed enhanced efficacy in the encapsulation of ibuprofen. This methodology could be expanded to combination drug therapy. **b** | Azobenzene-functionalized methacrylate was polymerized using atom transfer radical polymerization on a core with three azide arms and one with bromoisobutyryl bromide. An alkyne-func-tionalized chain transfer agent was subsequently clicked to the core, followed by radical addition-fragmentation chain transfer reaction to give an AB_3 miktoarm polymer. This then self-assembles into dual thermo- and photoresponsive micelles. **c** | N-isopropylacrylamide and 2-hydroxyethyl acrylate were first individually polymerized in an aqueous medium using Cu-mediated reversible deactivation radical polymerization (RDRP). The resulting solutions were subsequently mixed with N,N'-methylenebis(acrylamide) initiator, and RDRP continued to yield core crosslinked star mikotarm polymers. These easy-to-synthesize core crosslinked macromolecules self-assemble into stimuli-responsive higher order nanostructures.

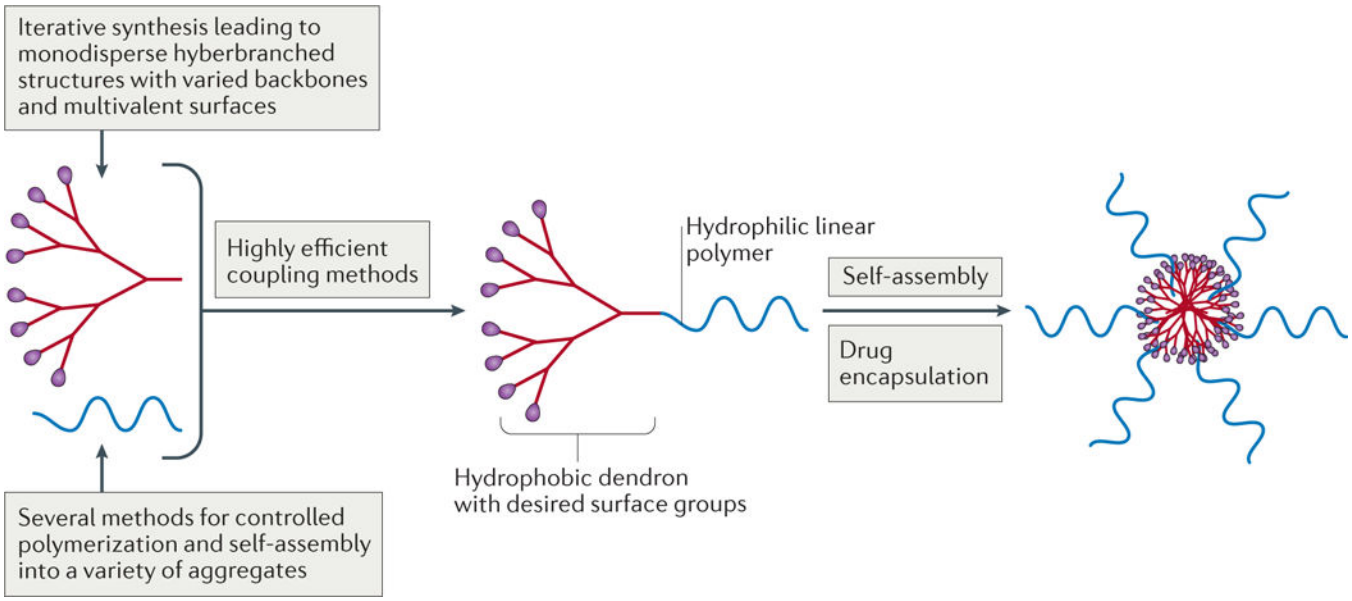

Figure 7 |. Telodendrimers combine important characteristics of hyperbranched and monodisperse dend ronswith those of linear polymers.

Dendrons and linear polymers with varied backbones can be synthesized using a large number of highly efficient synthetic methods described in FIG. 2. The multivalent surface of dendrons offers opportunities for conjugating any desired functional group, including therapeutics, imaging agents, and so on. Self-assembly into micelles then allows another drug to be physically encapsulated.

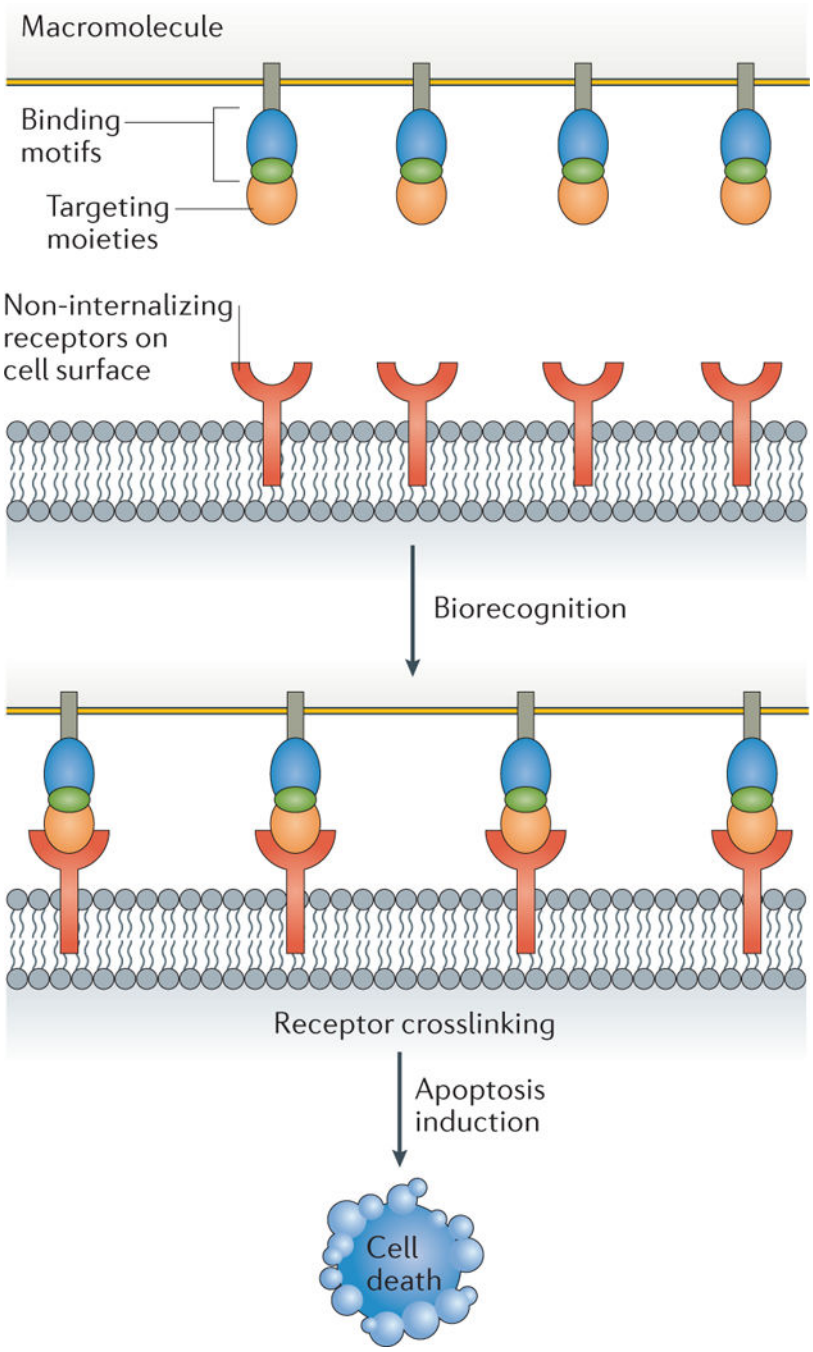

Figure 8 |. Polymer backbones are grafted with pendant targeting moieties that contain conjugated antiparallel coiled-coil peptides.

Biorecognition of these by the non-internalizing receptors on the cell surface causes cell receptor clustering (crosslinking), leading to cell death.

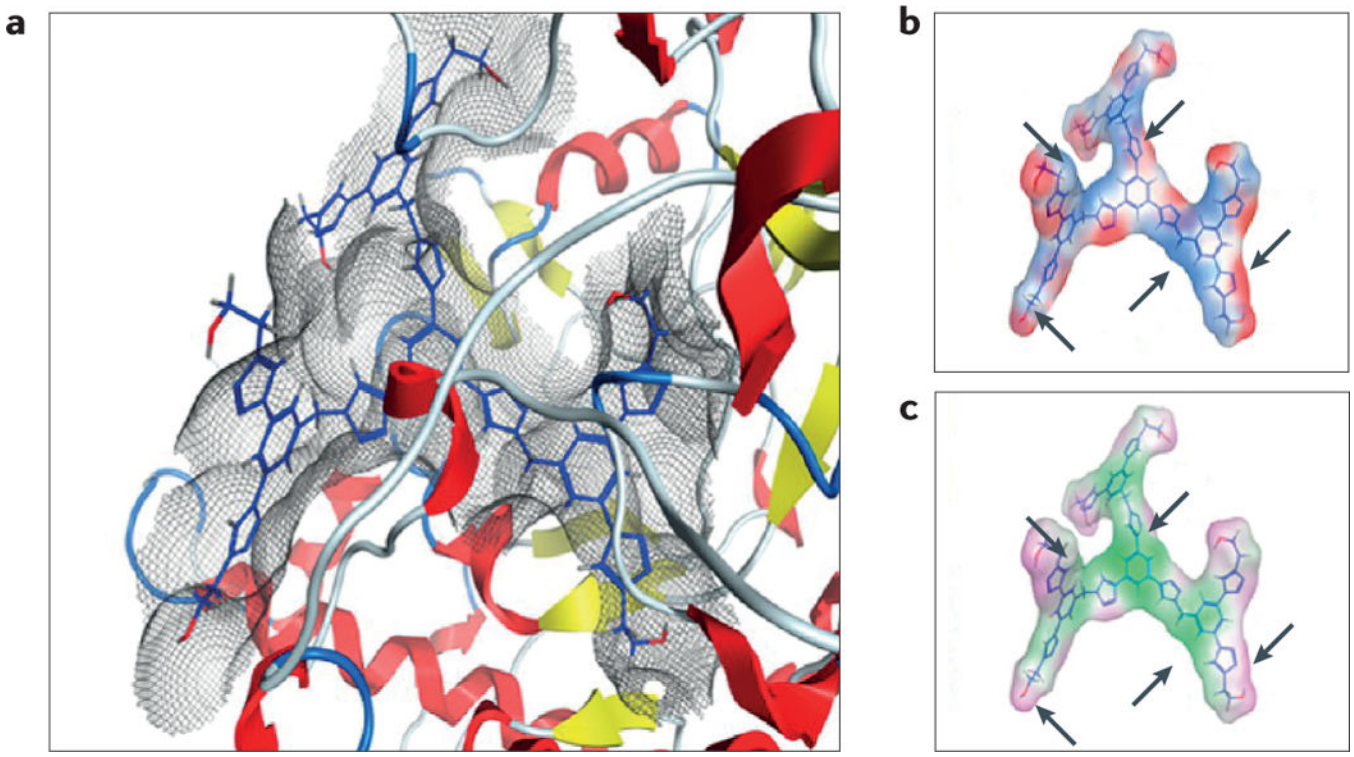

Figure 9 |. Anti-inflammatory activity of drug-free macromolecules.

Generation 1 dendrimer containing terminal hydroxyl groups fits into the active site of inducible nitric oxide synthase, and has favourable binding interactions: van der Waals (part a), electrostatic (part b; red is electronegative and blue is electropositive) and lipophilic (part c; green is lipophilic and purple is hydrophilic) surface maps. Part a depicts the lowest energy docking conformations, and parts b and c depict a comparison of the electrostatic and lipophilic surfaces. Arrows indicate the correlation between electropositive (blue) and lipophilic regions (green) of the molecule. Figure is adapted with permission from REF 187, American Chemical Society.

Table 1 |

Examples of nanoformulations in clinics and clinical trials

Trade name	Drug	Formulation	Use
In clinics			
Myocet	Doxorubicin	Liposomal	Metastatic breast cancer
Doxil	Doxorubicin	PEGylated liposomal	Leukaemia, lymphoma, carcinoma and sarcomas
DaunoXome	Daunorubicin	Liposomal	Kaposi sarcoma, leukaemia and non-Hodgkin lymphoma
DepoCyt	Cytarabine	Liposomal	Lymphomatous meningitis
Marqibo	Vincristine sulfate	Liposomal	Lymphoblastic leukemia
Visudyne	Verteporfin	Liposomal	Macular degeneration
Abraxane	Paclitaxel	Albumin-bound paclitaxel	Breast cancer and metastatic adenocarcinoma of the pancreas
Adagen	ADA	Linear polymer: monomethoxypoly(ethylene glycol)-ADA conjugate	Enzyme replacement therapy for severe combined immunodeficiency
Copaxone	Glatiramer acetate	Random copolymer of amino acids: glutamic acid, lysine, alanine and tyrosine	Multiple sclerosis
Oncaspar	L-Asparaginase	PEGylated L-asparaginase	Lymphoblastic leukemia
Pegasys	Interferon alfa-2a	PEGylated interferon	Hepatitis B and hepatitis C
Renagel	Sevelamer hydrochloride	Poly(allylamine-co-N,N’-diallyl-1,3-diamino-2-hydro xypropane) hydrochloride	Hypocalcemia and chronic kidney disease
Clinical trials			
Aroplatin	Bis-neodecanoate diaminocyclohexane platinum	Liposomal	Mesothelioma and colorectal carcinoma
Atragen	All-trans-retinoic acid	Liposomal	Promyelocytic leukemia and hematologic malignancies
Lipoplatin	Cisplatin	Liposomal	Non-small cell lung cancer adenocarcinomas
LEP-ETU	Paclitaxel	Liposomal	Breast, lung and ovarian cancer
Onco-TCS	Vincristine	Liposomal	Relapsed non-Hodgkin lymphoma
OSI-211	Lurotecan	Liposomal	Head, neck and ovarian cancer
SPI-077	Cisplatin	Liposomal	Head, lung and neck cancer
Narekt-102	Irinotecan	PEGylated liposomal	Breast and colorectal cancer
Livatag	Doxorubicin	Poly(isohexylcyanoacrylate)	Liver cancer
Paclitaxel poliglumex	Paclitaxel	Poly(L-glutamic acid)-paclitaxel conjugate	Breast, lung and ovarian cancer
Paclical	Paclitaxel	Micelles from surfactant-based derivative of retinoic acid (XR-17)	Breast, lung and ovarian cancer
PEG-docetaxel	Docetaxel	PEGylated docetaxel	Solid tumours

Trade name	Drug	Formulation	Use
VivaGel	SPL7013 astodrimer sodium	Polylysine dendrimer	In phase III trials for the treatment and prevention of bacterial vaginosis
DEP	DEP docetaxel	Polylysine dendrimer-docetaxel	In phase I clinical trials for the treatment of breast, lung and prostate cancer

ADA, adenosine deaminase; PEG, poly(ethylene glycol).