

Functional Degradable Nanogels by Reactive Precursor Block Copolymers for Immunotherapy

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Engineering stimuli-responsive nanomaterials can provide novel opportunities in medicine to address unmet medical needs, e.g. also in immunotherapy.¹ However, facile and straightforward access to multifunctional as well as biodegradable carriers is required. Self-assembly of amphiphilic block copolymers is often utilized to obtain micellar nanoparticles readily, yet with limited degree of functionalization, drug load or stability under physiological conditions. To that respect, we have introduced reactive precursor block copolymers that are functionalized and stabilized during their self-assembly process, e.g. by covalent incorporation of hydrophilic cross-links, fluorescent dyes or drugs into the micelle core affording functional degradable nanogels.²

One of the most versatile reactive precursor block copolymers we have been elucidation over the last years are based on RAFT polymerized pentafluorophenyl methacrylate (PFPPMA) with tri(ethylene glycol) methyl ether methacrylate (MEO₃MA). Their perfluorinated PFPPMA reactive ester block assures phase separate in polar aprotic solvents, e.g. DMSO, and provides micellar self-assemblies with amine reactive cores.³ During conversion with hydrophilic bis-amine crosslinkers under anhydrous conditions, the nanostructures are covalently stabilized while omitting PFP-ester hydrolysis. Moreover, by sequential addition of mono-amine entities further functionalities are introduced into the resulting core-crosslinked nanogel system while increasing its versatility in drug delivery: For instance, we have used cationic cross-linkers affording positively charged nanogels for siRNA delivery in antifibrotic therapy⁴ or CpG delivery in antitumor vaccination.⁵ Introducing disulfide or ketal-crosslinks guarantees nanoparticle degradability under reductive or acidic conditions present after cellular nanoparticle internalization.^{6,7} Interestingly, subcutaneous injection of non-charged ketal-crosslinked particles shows enhanced accumulation in draining lymph nodes (compared to non-crosslinked polymers) and facilitates local maturation of antigen-presenting cells, when TLR7/8 small molecule agonists are covalently ligated to the nanogels.⁸ They can successfully be applied as adjuvant during vaccination or even as immunotherapeuticum in cancer immunotherapy.

In addition, RAFT block copolymerization guarantees access to well-defined end groups which can be exploited towards bioconjugation with peptide or protein antigens via vinylsulfone or click chemistry.^{5,9} Moreover, decorated with targeting single chain antibodies (nanobodies) promotes nanogel delivery into special immune cell subpopulations (e.g. tumor-associated macrophages TAM) in the tumor milieu.

Finally, squaric ester amides have recently been utilized as amine sensitive groups for protein conjugation under aqueous conditions.¹⁰ Novel reactive precursor block copolymers based on squaric ester amide monomers will be introduced that allow conjugation of water soluble drugs, e.g. bisphosphonates, to squaric amide based nanogels (squarogels) for TAM modulation.

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Lutz Nuhn graduated in biomedical chemistry at the Johannes Gutenberg-University Mainz (Germany) in 2010. In 2008/09, he practiced first research experience at MIT with Robert Langer and Daniel G. Anderson. For his PhD he joined the groups of Rudolf Zentel (Mainz, Germany) and Prof. Kazunori Kataoka (Tokyo, Japan) to obtain his degree in 2014. Afterwards, he worked as postdoctoral associate in the group of Bruno G. De Geest with Richard Hoogenboom at Ghent University (Belgium). Since summer 2017 he has joined the group of Tanja Weil at the Max Planck Institute for Polymer Science (Mainz, Germany) as junior group leader.



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