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Title: Mannose-Decorated Multicomponent Supramolecular Polymers Trigger Effective Uptake into Antigen-Presenting Cells

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Mannose-Decorated Multicomponent Supramolecular Polymers Trigger Effective Uptake into Antigen-Presenting Cells

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Abstract: We describe a modular route to prepare functional self-assembling dendritic peptide amphiphiles decorated with mannosides (Man) to effectively target antigen-presenting cells such as macrophages. The monomeric building blocks were equipped with tetraethylene glycols (TEG) or labelled with a Cy3 fluorescent probe. Experiments on the uptake of the multifunctional supramolecular particles into murine macrophages (Mϕs) were monitored by confocal microscopy and fluorescence-activated cell sorting (FACS). Mannose-decorated supramolecular polymers trigger a significantly higher cellular uptake and distribution, compared to TEG carrying bare polymers. No cytotoxicity or negative impact on cytokine production of the treated Mϕs was observed, emphasizing their biocompatibility. The modular nature of the multicomponent supramolecular polymer co-assembly protocol is a promising platform to develop fully synthetic multifunctional vaccines, for example in cancer immunotherapy.

Vaccination and immunization against bacterial or viral pathogens is one of biggest achievements in human healthcare. Although an immune response can also be generated against endogenous diseases like cancer[1] there is a need for more elaborate and potent vaccine systems to activate specific immune cell types. A modular chemical platform, which allows both multivalent targeting of antigen-presenting cells (APCs such as macrophages[2] and dendritic cells[3]) and presentation of multiple immunogenic epitopes will facilitate the investigation of the underlying mechanisms of the immune response. In view of the synthetic accessibility of polyvalent and multifunctional epitopes, classical iterative postfunctionalization or copolymerization strategies in covalent polymer synthesis suffer from limitations regarding the degree of functionalization. Therefore, total polymer composition results in poor batch to batch reproducibility. In the case of supramolecular polymers, simple mixing of different well-defined molecular building blocks guarantees full flexibility and facile access to screen and optimize the composition of multifunctional copolymers.[4] In contrast to conventional polymers, where monomers are connected via irreversible covalent bonds, supramolecular polymers are held together by a multitude of non-covalent interactions.[4] E. W. Meijer and coworkers have shown that benzene-tricarboxamides (BTA), bearing amino acid side arms, self-assemble into multifunctional polymer arrays in water, and were used to present RGDS and PHSRN integrin binding peptides, as well as Gd^{III} MRI labels at the periphery.[5] Alternatively, large dodecyl chains in the arms also provide sufficient hydrophobicity to protect the hydrogen bonding supramolecular assemblies, for example bearing cationic side chains which are used to condense siRNA and hydrophobic guest molecules.[6] Brunsveld used bipyridine units connected to BTAs in order to direct the self-assembly into columnar supramolecular copolymers with a tunable surface density of mannose units for the clustering and detection of *E. coli* bacteria or to assemble wires of proteins via surface ligation.[7]

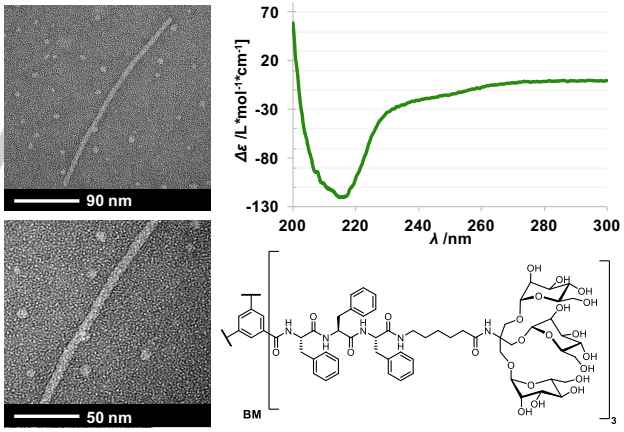

Figure 1. On the left: negative stained transmission electron microscopy image obtained from a 25 μM aqueous solution of the self-assembled mannosylated prototype monomer **BM**; on the right: circular dichroism spectra of the dentritic peptide amphiphile **BM** in 60 μM aqueous buffered solution.

Here, we report the use of BTA and triazine branched nonaphenylalanines that direct the supramolecular polymerization into anisotropic particles of up to 300 nm in length (Figure 1). Given their resemblance to rod-like virus particles, we were intrigued to prepare carbohydrate decorated supramolecular polymers via the co-assembly of mannose functional monomers, shielding dendritic TEG chains as protein repellent units and fluorescent labels, in order to trigger the selective cellular uptake into APCs, specifically murine Mϕs.

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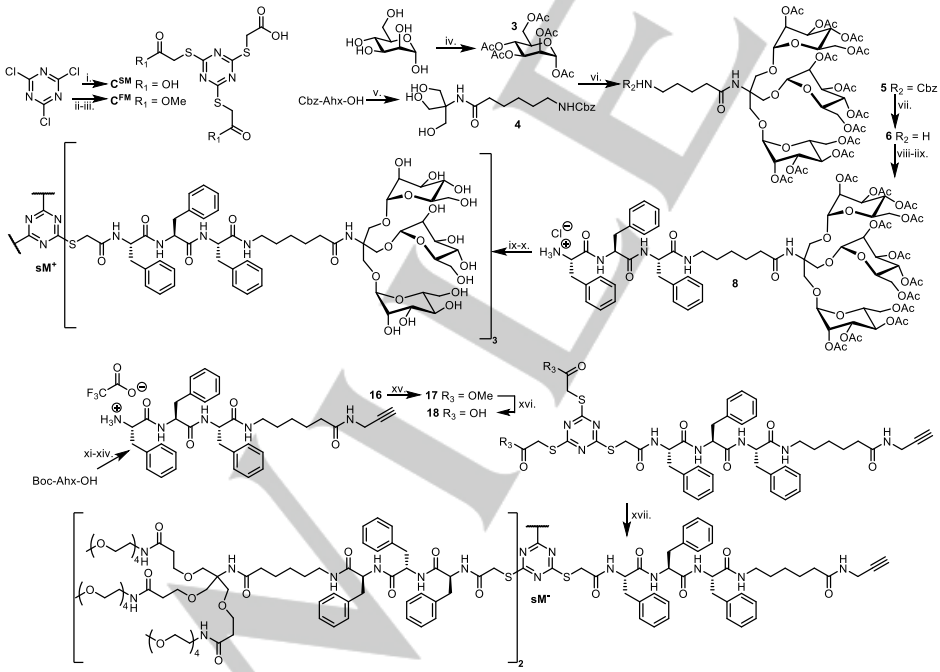
The first objective was the introduction of a targeting motif into the monomeric self-assembling architecture. Carbohydrates serve as water-solubilizing, as well as molecular recognition moieties. Therefore, the extensively used tris (hydroxymethyl)aminomethane (TRIS) based dendron was equipped with mannose to obtain triple mannosylated TRIS-Man_3, which aims to introduce solubilizing properties as well as a similar sterical demand compared to the dendritic TEG chains and thus install colloidal stability of the supramolecular polymers.[8] Mannose is known for its targeting properties to cells of the innate immune system, inter alia, Mϕs and dendritic cells which expose mannose recognizing receptors (MR) on their cell surface and play a key role in host defense. Upon binding of mannosylated compounds, these induce receptor-mediated endocytosis.[9] Note that due to the importance of carbohydrate-protein interactions in biological processes, the polymer science[10] and supramolecular communities[7a, 11] has reported the synthesis of a variety of covalent macromolecular architectures and scaffolds as artificial glycoconjugates that mimic the multivalent display[12] of carbohydrates. In a first attempt to prepare mannose-decorated supramolecular polymers, BTA-dendritic nonaphenylalanine scaffolds were equipped with TRIS-Man_3. To this end, the glycosyl donor **3** was prepared from D-mannose by acetylation in pyridine/acetic anhydride. Acceptor **4** was obtained by amidation of TRIS with Cbz-protected aminohexanoic acid (Ahx) using EEDQ as coupling reagent. The glycosylation was catalyzed at 0 °C in DCM with BF_3 etherate and gave moderate yields with high stereoselectivity. The optimized conditions for the removal of the Cbz group were a solvent mixture of dioxane/TFA and Pd/C (10 wt%) as hydrogenation catalyst. The obtained TRIS-Man_3 **6** was coupled to Boc-Phe_3-OH **1a** with PyBOP, HOAt and DIPEA in DMF. After removal of the Boc group with TFA followed by consecutive lyophilization steps with aqueous HCl, the saccharide functionalized arm **8** was isolated. After coupling of **8** to the trimesic acid with PyBOP and DIPEA in DMF at room temperature, and a final deprotection of the mannoside by treatment with freshly prepared sodium methoxide in methanol, the amphiphilic glycopeptide **BM** was obtained. In aqueous buffer, **BM** self-assembles into supramolecular homopolymeric nanorods with a length of up to 300 nm (Figure 1). Circular dichroism spectroscopic analysis of these supramolecular homopolymers, gives rise to a strong negative band at λ = 216 nm, indicative of ß-sheet directed self-assembly of the hydrophobic oligophenylalanine core.[8a, 8b]

In order to provide access to a variety of structurally diverse functional supramolecular monomers, including the possibility for post-functionalization with imaging labels, an alternative synthetic route for a C_2-symmetric functional monomer (**fM**) was devised using a dendritic core, extended with triphenylalanyl moieties $(Phe)_3$ and the Ahx spacer bearing a terminal alkyne group. The latter allows to address one side-arm of the building blocks via copper-mediated azide alkyne coupling (CuAAC),[13] as functionalization site. Using cyanuric chloride as a branching point thioglycolic acid and its methyl ester were sequentially attached to create a C_2-symmetric core. In a two-step procedure, the orthogonally stably protected core $\mathbf{C^{FM}}$ was synthesized, first by double substitution using two equivalents of methyl-2-thioglycolate and potassium carbonate. The third substitution on the chlorotriazine **2** was carried out with thioglycolic acid and DIPEA at elevated temperature (40 °C). Treatment of cyanuric chloride with three equivalents of 2-thioglycolic acid at 60 °C in acetonitrile and DIPEA gave the trisubstituted core $\mathbf{C^{SM}}$. Coupling of the alkyne terminated triphenylalanine **16** on one arm of $\mathbf{C^{FM}}$, followed by methyl ester hydrolysis using 0.1 M LiOH in THF, double amidation with TRIS-Man_3 decorated triphenylalanine **8** and subsequent deprotection with NaOMe, turned out to be a straightforward strategy to afford the alkyne-functional mannosylated monomer $\mathbf{fM^+}$. Using the TRIS-$(TEG)_3$ carrying triphenylalanine **12**, the alkyne-functionalized TEGylated monomer $\mathbf{fM^-}$ was obtained, that lacks targeting motifs. In a final step, both monomers $\mathbf{fM^+}$ and $\mathbf{fM^-}$ were conjugated with a Sulfo-Cy3 fluorescent azide dye via CuAAC in degassed DMSO, aqueous $CuSO_4 \times 5H_2O$, sodium ascorbate and tris(benzyltriazolylmethyl)amine (TBTA) as chelating agent to stabilize the Cu(I) species generated *in situ*.



Scheme 1. Scheme for the synthesis of selected triazine based structural and functional monomers (i). HSAcOH, DIPEA, MeCN, 60%, (ii). HSAcOMe, K_2CO_3, THF, 58% (iii). HSAcOH, DIPEA, MeCN, 56%. (iv). pyridine, Ac_2O, DMAP, quant. (v). TRIS, EEDQ, EtOH, 60% (vi). $BF_3 \times Et_2O$, DCM, 40% (vii). dioxane, TFA, Pd/C, H_2, 79% (viii). Boc-Phe_3-OH **1a**, PyBOP, HOAt, DIPEA, 66% (iix). TFA/DCM, TIS, quant. (ix). $\mathbf{C^{SM}}$, PyBOP, DIPEA, DMF, 88% (x). NaOMe, MeOH, quant. (xi). HATU, HOAt, DMF, 56% (xii).DCM/TFA, 97% (xiii). **1a**, PyBOP, HOAt, NMM, DMF, 95% (xiv). DCM/TFA, TIS, 96% (xv). $\mathbf{C^{FM}}$, HATU, HOAt, DIPEA, DMF, quant. (xvi). LiOH 0.1 M, THF 72% (xvii). Dnd-Ahx-Phe_3-NH_2 **12**, PyBOP, HOBt, DIPEA, DMF, 79%.

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The reaction took place at 40 °C (80 °C) within 2 days. Excessive copper was removed by passing the reaction mixture through a short bed of IRC-148 resin and subsequent size exclusion chromatography on *Sephadex* LH-20 in DMF. Structural C_3-symmetric monomers that lack the alkyne moiety and carry either three TRIS-$(TEG)_3$ dendrons as solubilizing chains at the periphery (**sM$^-$**), or three dendritic TRIS-Man_3 units (**sM$^+$**) were obtained via amidation of the trisubstituted core **C^{SM}** using the same conditions as described above for the C_2-symmetric building blocks.

The supramolecular polymers were characterized in aqueous solution with CD spectroscopy (Figures S2) and TEM (Figures S3), which both confirmed the self-assembly into nanorod-like β-ordered materials, irrespective of the functional group density in the periphery. These results confirm the high robustness and fidelity of the dendritic nonaphenylalanine-driven architectures, as already indicated for the simpler building block **BM**. Encouraged by these results the cellular uptake behavior of self-assembled mannosylated supramolecular polymers by murine Mϕs *in vitro* was tested. The self-assembled Cy3-labeled building blocks with (**FM$^+$**) and without $TRISMan_3$ units (**FM$^-$**), were added as 25 μM monomer solutions to cultured bone marrow-derived Mϕs differentiated in M-CSF-conditioned medium at a concentration of 25 μM and incubated at 4 °C for 2 h to reduce unspecific binding. Subsequently, Mϕs were co-stained with a fluorophore-labelled mannose receptor (MR, CD206) antibody to determine the extent of MR expression. Binding of the polymeric **FM$^-$** and **FM$^+$** was determined by FACS analysis (for details see SI) which revealed a marginal unspecific absorption of **FM$^-$** (1%) while 46% of Mϕs stained positive after incubation with mannose-decorated **FM$^+$** (Figure S4A). The high selectivity was corroborated by plotting the mean fluorescence intensity, which was more than an order of magnitude higher after treatment with mannosylated **FM$^+$**, compared to Mϕs that were incubated with TEGylated **FM$^-$** (Figure S4B).

In order to confirm the FACS data, we performed laser scanning confocal microscopy (LSCM) and further examined the receptor-mediated uptake of the **FM$^+$** particles after binding to the MR. Mϕs were prepared as described above for FACS analyses. In addition, the cell nuclei were stained with DAPI as blue fluorescent dye (for details see SI). The LSCM images clearly show that the mannosylated and Cy3 labelled building block **FM$^+$** is internalized into the Mϕs (Figure 2A). In contrast, no uptake was observed for the TEG-bearing and Cy3 labelled building block **FM$^-$** (Figure 2B), confirming the MR-mediated endocytosis. Encouraged by these findings, mixing experiments of monomers into multicomponent copolymers were performed, in order to evaluate the potential of these rod-like particles as modular platform in the development of multifunctional targeted synthetic vaccines. A 1:1 mixture of the fluorescence (Cy3) labelled TEG-bearing **fM$^-$** was used, in combination with the mannosylated, but non-labelled monomer **sM$^+$**. LSCM images showed that TEGylated Cy3-labelled self- assembled polymeric **FM$^-$** were taken up by Mϕs after co-

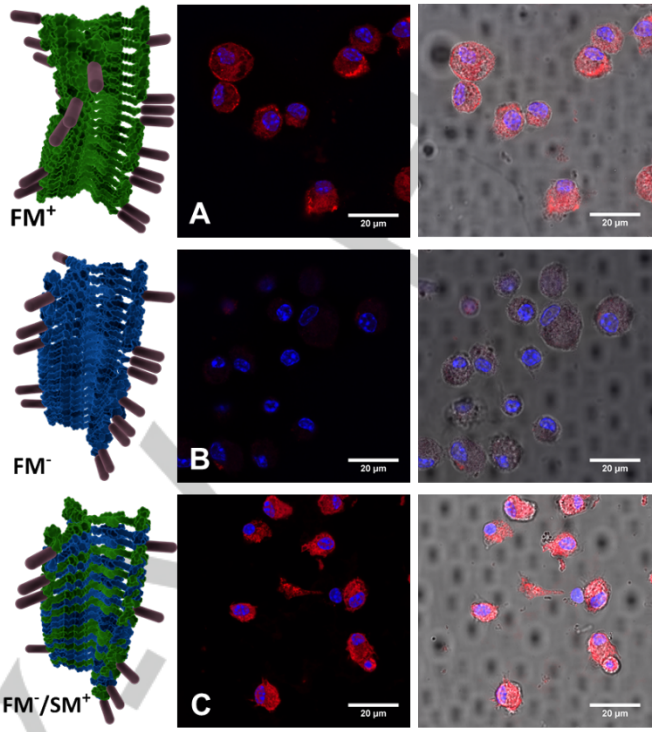

Figure 2. Confocal microscopy images of murine Mϕs incubated with self-assembled monomers (all added at building block concentrations of 25 μM) in growth media at 4 °C, **A**: Cy3 labelled mannosylated polymer (**fM$^+$**); **B**: Cy3 labelled polymer without mannose (**fM$^-$**), **C**: co-assembled 1:1 mixture of non-fluorescent mannosylated **sM$^+$** and Cy3 labelled TEGylated **fM$^-$** containing no mannose.

assembly with mannosylated **SM$^+$** (Figure 2C) indicating that these two components form stable supramolecular polymers under physiological conditions. Control experiments using homopolymeric **SM$^+$** and **SM$^-$** were performed to exclude unspecific interactions between the Cy3 dye and the hydrophobic core of the peptide supramolecular polymers. Both components were mixed with free Cy3 dye and incubated with Mϕs. Close inspection of the LSCM images did not reveal any Cy3-related fluorescence (Figures S5 A-C). Using LSCM we further confirmed that the cellular uptake in macrophages triggered by mannose presentation on supramolecular homo- and copolymers at 37 °C is undistinguishable from the uptake at 4 °C (Figures S5 D-F). In conclusion, LSCM and FACS analyses provide strong evidence that the copolymers are stable and that the incorporation of mannosylated monomers induces the internalization into Mϕs via a mannose receptor-mediated pathway.

For biomedical applications of nanomaterials, cytotoxicity is a crucial factor that limits the applicability of new drugs and their carriers. Therefore, Mϕs were stimulated with lipopolysaccharide (LPS, 100 ng mL^{-1}) in the absence and presence of **FM$^-$**, **FM$^+$** and **FM$^-$/SM$^+$** for 24 h at 37 °C. Subsequently, FACS analyses in combination with a fixable viability dye revealed that these functional supramolecular polymers exhibited no cytotoxicity against Mϕs (Figure S6). In order to further exclude negative effects on the bioactivity of Mϕs, the resulting supernatants were tested for the production of inflammatory cytokines interleukin-6 (IL-6)[14] and tumor necrosis factor alpha (TNF-α)[15], known to be

secreted by Mϕ immediately after LPS-mediated activation. No negative impact on the cytokine production was observed. Rather, the treatment of the Mϕs has led to an increased production of TNF-α while no increased levels of IL-6 were detected, which suggested that the Mϕs become activated by the receptor mediated uptake of mannosylated supramolecular particles (Figure S7). These findings are promising for the development of self-assembled multifunctional and fully synthetic glycopeptide vaccines.

Conclusions

Nanorod-like supramolecular polymers bearing a high-density shell of mannosides or ethylene glycol moieties at their surface were prepared via the self-assembly of functional comonomers, which were further labelled with a fluorescent probe using copper-mediated azide alkyne coupling. The resulting labelled polymers were used to monitor cellular uptake into bone marrow-derived murine Mϕs. A dendritic tetraethylene glycol and fluorescence labeled homopolymeric **FM**$^{-}$ did not show measurable internalization into Mϕs using confocal microscopy. However, co-assembly of a fluorescent TEGylated monomer **fM**$^{-}$ with a non-fluorescent mannosylated **sM**$^{+}$ into supramolecular **FM**$^{-}$**/SM**$^{+}$ copolymers triggered cellular uptake. Surface mannose units thus facilitate efficient cellular uptake via a mannose receptor-mediated pathway, as confirmed by FACS analyses. Furthermore, the incubation of the multifunctional supramolecular copolymers with Mϕs did not negatively affect the cell viability or production of proinflammatory cytokines. The copolymerization properties will allow cross-presentation of various antigens, saccharides and immunostimulants which are necessary to develop potent multifunctional anti-tumor vaccines. The nanorod-shaped viromimetic particles are a powerful and modular platform for the development of fully synthetic vaccines, that effectively target antigen-presenting cells and are capable of inducing a strong immune response.

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Keywords: supramolecular polymer • multicomponent biomaterials • self-assembly • mannose receptor-targeting • immune cells

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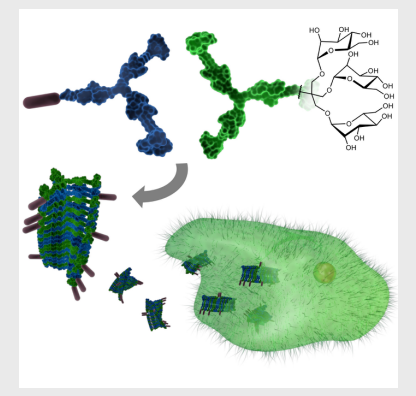
A modular route is presented to prepare multifunctional supramolecular polymers based on self-assembled dendritic peptide amphiphiles decorated with mannosides to effectively target antigen-presenting cells such as macrophages. The multicomponent co-assembly protocol is a powerful platform for the development of fully synthetic multifunctional vaccines.



D. Straßburger, N. Stergiou, M. Urschbach, H. Yurugi, D. Spitzer, D. Schollmeyer, E. Schmitt, P. Besenius**

Page No. – Page No.

Mannose-Decorated Multicomponent Supramolecular Polymers Trigger Effective Uptake into Antigen-Presenting Cells