Supporting Information

Scaling Behavior of Dendritic Nanoparticle Mobility in Semidilute Polymer Solutions

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Contents

S1. Synthesis and characterization of ^{19}F-labeled poly(propylene imine) (PPI) based nanoparticles

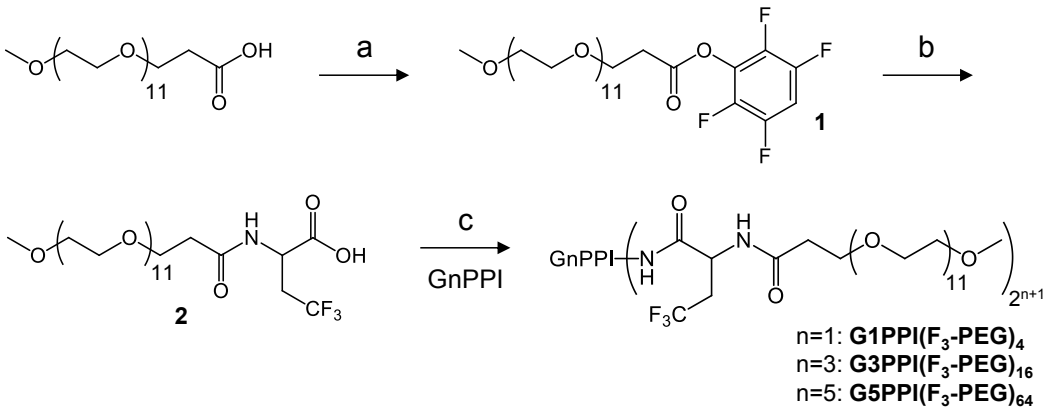
Materials. All reagents, chemicals, materials and solvents were obtained from commercial sources, and were used as received: Biosolve, Merck and Cambridge Isotope Laboratories for (deuterated) solvents; Aldrich, Acros, ABCR, Merck, Fluorochem and Fluka for chemicals, materials and reagents. SyMO-Chem owns stocks of poly(propylene imine) (PPI) dendrimers, and G1PPI$(NH_2)_4$, G3PPI$(NH_2)_{16}$ and G5PPI$(NH_2)_{64}$ have been used as starting compounds for the described conversions. 4,7,10,13,16,19,22,25,28,31,34,37-Dodecaoxaoctatriacontanoic acid was obtained from Polypure. All solvents were of AR quality. Moisture or oxygen-sensitive reactions were performed under an Ar atmosphere. Hygroscopic compounds (e.g. those containing ethylene oxide chains) were stored under vacuum in a desiccator over P_2O_5. Bio-Beads S-X1 was obtained from Bio-Rad Laboratories. 3,4,5-Tris((17-azido-3,6,9,12,15-pentaoxaheptadec-1-yl)oxy) benzoic acid was prepared according to Vugts et al.[1]

Methods. ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR spectra were recorded on a Varian Mercury (400 MHz for ^{1}H-NMR, 100 MHz for ^{13}C-NMR, and 376 MHz for ^{19}F-NMR) spectrometer at 298 K. Chemical shifts are reported in ppm downfield from TMS at r.t. using deuterated chloroform ($CDCl_3$) as a solvent and internal standard unless otherwise indicated. Abbreviations used for splitting patterns are s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad. IR spectra were recorded on a Perkin Elmer 1600 FT-IR (UATR). Preparative size exclusion chromatography was performed using Bio-Rad Bio-Beads S-X1 (200-400 mesh). MALDI-TOF MS was measured on a Bruker Autoflex Speed. GC-MS was performed using a Shimadzu GC-2010 on a Phenomenex Zebron ZB-5MS column (i.d. = 0.25 mm). LC-MS was performed using a Shimadzu LC-10 AD VP series HPLC coupled to a diode array detector (Finnigan Surveyor PDA Plus detector, Thermo Electron Corporation) and an Ion-Trap (LCQ Fleet, Thermo Scientific) where ions were created via electrospray ionization (ESI). Analyses were performed using a Alltech Alltima HP C_{18} 3µ column using an injection volume of 1-4 µL, a flow rate of 0.2 mL min^{-1} and typically a gradient (5% to 100% in 10 min, held at 100% for a further 3 min) of CH_3CN in H_2O (both containing 0.1% formic acid) at 298 K. Preparative RP-HPLC (CH_3CN / H_2O with 0.1% formic acid) was performed using a Shimadzu SCL-10A VP coupled to two Shimadzu LC-8A pumps and a Shimadzu SPD-10AV VP UV-vis detector on a Phenomenex Gemini 5µ C_{18} 110A column. GPC (DMF/LiBr) was performed on a Polymer Laboratories PL-GPC 50 Plus using a Shodex KD-804 column (8 mm i.d. × 300 mm) conditioned at 50 °C, employing DMF containing 0.10 mM LiBr and 0.25 % v/v H2O as eluent, and applying a differential refractive index detector. GPC (aqueous solution) was performed using a Tosoh

Bioscience TSKgel G3000PWXL column (7.8 mm i.d × 300 mm) with 0.10 M citric acid containing 0.25 % w/v NaN3 as eluent, using a differential refractive index detector. NMR relaxometry was performed on a Bruker Avance II spectrometer, equipped with a Bruker diff25 probe, at 7.0 T (300 MHz for ^{1}H and 282 MHz for ^{19}F), on ~1 mM dendritic particles in water at 293 K. The probe was equipped with a 10-mm RF insert that could be tuned to both ^{1}H and ^{19}F. Sample volume was chosen as to not exceed the NMR coil volume. $\boldsymbol{T}_2$ was measured by a frequency-domain CPMG experiment with an inter-echo time of 1 ms. In the ^{1}H case, the CPMG experiment was preceded by a PFG NMR-type experiment with magnetic field gradients strong enough to attenuate the prominent water signal significantly ("diffusion editing"), so that the ^{1}H signal of the micelles, which diffuse ~100 times slower, was of comparable intensity.

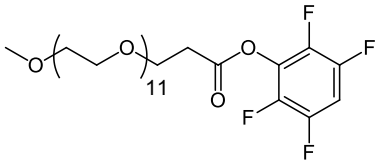
S1.A. Nanoparticles with generation 1, 3 and 5 PPI-dendritic cores: G1PPI(F_3-PEG)$_4$, G3PPI(F_3-PEG)$_{16}$, G5PPI(F_3-PEG)$_{64}$

Synthetic Procedures.



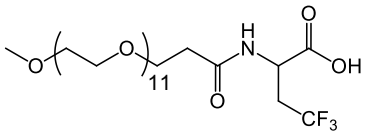
Scheme S1.1. Synthesis of fluorinated dendritic nanoparticles. (a) 2,3,5,6-tetrafluorophenol, pyridinium p-toluenesulfonate, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, dichloromethane, 2 h, r.t., 100%; (b) 2-amino-4,4,4-trifluorobutyric acid, 2M NaOH, dioxane, 2 h, r.t., 75%; (c) GnPPI dendrimer, N,N-diisopropylethylamine, PyBOP, dichloromethane, 1½ h, r.t., 96% (n=1), 95% (n=3), 90% (n=5).

2,3,5,6-Tetrafluorophenyl 4,7,10,13,16,19,22,25,28,31,34,37-dodecaoxaoctatriacontanoate (1)



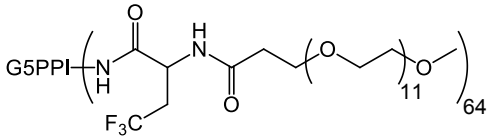
In a 10 mL round-bottom flask, 4,7,10,13,16,19,22,25,28,31,34,37-dodecaoxaoctatriacontanoic acid (104 mg, 0.17 mmol), 2,3,5,6-tetrafluorophenol (33 mg, 0.19 mmol, 1.1 eq), pyridinium ***p***-toluenesulfonate (5 mg, 19 µmol, 0.1 eq) and dichloromethane (2 mL) were combined. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (37 mg, 0.19 mmol, 1.1 eq) was added as a solid and the reaction mixture was stirred at room temperature for 2 h. Chloroform (50 mL) was added and the solution was washed with sat. $NaHCO_3$ (20 mL) and brine (2 × 20 mL). The organic layer was dried over $MgSO_4$, filtrated and the solvent was removed ***in vacuo***. This yielded pure **1** (131 mg, 0.17 mmol, 100%) as a colorless oil, which was used immediately in the next step. ^{1}H-NMR: δ = 7.00 (qn, 1H, Ar***H***), 3.88 (t, 2H, C***H***$_2$COO), 3.78-3.54 (m, 44H, C***H***$_2$O), 3.39 (s, 3H, C***H***$_3$), 2.96 (t, 2H, C***H***$_2$CH$_2$COO). ^{19}F-NMR: δ = -139.0 (m, 2F, Ar***F***), -152.8 (m, 2F, Ar***F***).

2-(2,2,2-Trifluoroethyl)-3-aza-4-oxo-7,10,13,16,19,22,25,28,31,34,37,40-dodecaoxahentetracontanoic acid (2)



In a 5 mL tube flask, 2-amino-4,4,4-trifluorobutyric acid (250 mg, 1.54 mmol) was dissolved in 2 M NaOH (770 µL, 1 eq). To the resulting clear solution **1** (1.22 g, 1.66 mmol, 1.1 eq) was added in six portions over 1 h, while each addition was followed by the addition of sat. NaOH (35 µL) to ensure that pH > 9.5 (the last aliquot of **1** was added as a solution in dioxane). The mixture was stirred at r.t. for another 45 min after which concentrated HCl was added up to pH = 1. Subsequently, 1 M HCl (80 mL) was added and the aqueous phase was extracted with chloroform (4 × 30 mL). The combined organic layers were dried using $MgSO_4$, filtrated and the solvent was removed ***in vacuo***. The compound was purified using column chromatography (flash SiO_2) using an elution gradient of 3% MeOH in chloroform to 20% MeOH in chloroform to {20% MeOH + 1% formic acid} in chloroform. Alternatively, the compound was purified by means of preparative RP-HPLC using an elution gradient of 31% to 35% CH_3CN in H_2O containing 0.1% formic acid (detection at $\boldsymbol{\lambda}$ = 200 and 254 nm). This yielded pure **2** (840 mg, 1.15 mmol, 75%) as a colorless oil. ^{1}H NMR: $\boldsymbol{\delta}$ = 7.61 (d, 1H, N***H***), 4.77 (m, 1H, C***H***), 3.76-3.54 (m, 46H, OC***H***$_2$), 3.38 (s, 3H, OC***H***$_3$), 2.89 (m, 1H, C***H***HCF$_3$), 2.75 (m, 1H, CH***H***CF$_3$), 2.54 (m, 2H, C***H***$_2$CO). ^{13}C-NMR: $\boldsymbol{\delta}$ = 172.0, 171.0, 125.9 (q), 71.8, 70.44, 70.42, 70.38, 70.35, 70.3, 70.2, 66.9, 58.9, 47.4, 36.4, 34.9 (q). ^{19}F-NMR: $\boldsymbol{\delta}$ = -63.1. LC-MS: ***m/z*** = 728.6 [M+H]$^+$, 750.7 [M+Na]$^+$ (calcd 727.4 for $C_{30}H_{56}F_3NO_{15}$). FT-IR (ATR): $\boldsymbol{\nu}$ (cm^{-1}) = 3319, 2870, 1736, 1672, 1535, 1452, 1381, 1349, 1326, 1294, 1252, 1200, 1098, 1028, 948, 846, 805, 672, 659.

G5PPI(F$_3$-PEG)$_{64}$

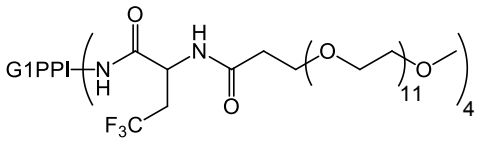


In a 100 mL round-bottom flask, G5PPI(NH$_2$)$_{64}$ (97 mg, 13.5 µmol), **2** (757 mg, 1.0 mmol, 1.2 eq per NH$_2$) and ***N,N***-diisopropylethylamine (550 µL, 3.1 mmol, 3 eq to **2**) were dissolved in dichloromethane (12 mL). After the addition of PyBOP (558 mg, 1.0 mmol, 1.2 eq per NH$_2$) and dichloromethane (2 mL) the solution was stirred at room temperature for 1½ h. Chloroform (150 mL) was added and the solution was washed with 0.1 M NaOH (40 mL). The organic layer was dried using Na_2SO_4, filtrated and the solvent was removed ***in vacuo***. Preparative size-exclusion chromatography (Bio-Beads SX-1, 10% MeOH in $CHCl_3$) yielded pure **G5PPI(F$_3$-PEG)$_{64}$** (634 mg, 12.1 µmol, 90%) as a slightly orange oil. ^{1}H-NMR: $\boldsymbol{\delta}$ = 8.35 (br, 32H, N***H***CO), 8.21 (br, 32H, N***H***CO), 7.89 (br, 64H, N***H***CO), 5.08 (br, 32H, C***H***), 4.95 (br, 32H, C***H***), 3.78-3.52 (m, 2944H, C***H***$_2$O), 3.38 (s, 192H, C***H***$_3$),

3.23 (br, 128H, C***H***$_2$NHCO), 2.80-2.14 (br, 628H, C***HH***CF$_3$, C***H***$_2$NC***H***$_2$, C***H***$_2$CONH), 1.72-1.38 (br, 252H, NCH$_2$C***H***$_2$CH$_2$N, NCH$_2$C***H***$_2$C***H***$_2$CH$_2$N). ^{1}H-NMR (D$_2$O): ***δ*** = 4.69 (m, 64H, C***H***), 3.84-3.61 (m, 2944H, C***H***$_2$O), 3.40 (s, 192H, C***H***$_3$), 3.28 (m, 64H, C***H***$_2$NHCO), 3.17 (m, 64H, C***H***$_2$NHCO), 2.84 (m, 64H, C***H***HCF$_3$), 2.74-2.36 (m, 564H, CH***H***CF$_3$, C***H***$_2$NC***H***$_2$, C***H***$_2$CONH), 1.68 (br, 252H, NCH$_2$C***H***$_2$CH$_2$N, NCH$_2$C***H***$_2$C***H***$_2$CH$_2$N). ^{13}C-NMR: ***δ*** = 171.4, 170.0, 125.7 (q), 71.9, 70.5, 70.3, 70.1, 67.1, 59.0, 52.1 (br), 50.6 (br), 47.5 (br), 37.6 (br), 36.5 (br), 26.6 (br), 24.5 (br). ^{19}F-NMR: ***δ*** = -64.0. ^{19}F-NMR (D$_2$O): ***δ*** = -63.9. FT-IR (ATR): ***ν*** (cm^{-1}) = 3286, 2882, 1648, 1539, 1466, 1345, 1279, 1261, 1242, 1200, 1110, 964, 949, 844, 630.

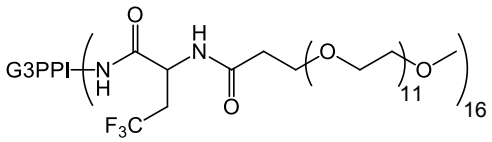
G1PPI(F$_3$-PEG)$_4$ and **G3PPI(F$_3$-PEG)$_{16}$** were synthesized according to a similar procedure as described for **G5PPI(F$_3$-PEG)$_{64}$.**

G1PPI(F$_3$-PEG)$_4$



Pure **G1PPI(F$_3$-PEG)$_4$** was obtained as a yellowish oil in 96% yield. ^{1}H-NMR: ***δ*** = 7.70 (br, 4H, N***H***CO), 7.56 (br, 4H, N***H***CO), 4.81 (br, 2H, C***H***), 4.69 (br, 2H, C***H***), 3.84-3.52 (m, 184H, C***H***$_2$O), 3.37 (s, 12H, C***H***$_3$), 3.29 (br, 8H, C***H***$_2$NHCO), 2.90-2.28 (br, 28H, C***HH***CF$_3$, C***H***$_2$NC***H***$_2$, C***H***$_2$CONH), 1.88-1.32 (br, 12H, NCH$_2$C***H***$_2$CH$_2$N, NCH$_2$C***H***$_2$C***H***$_2$CH$_2$N). ^{1}H-NMR (D$_2$O): ***δ*** = 4.67 (dd, 4H, C***H***), 3.84-3.62 (m, 184H, C***H***$_2$O), 3.40 (s, 12H, C***H***$_3$), 3.32 (m, 4H, C***H***$_2$NHCO), 3.23 (m, 4H, C***H***$_2$NHCO), 2.92-2.55 (m, 28H, C***HH***CF$_3$, C***H***$_2$NC***H***$_2$, C***H***$_2$CONH), 1.78 (m, 8H, NCH$_2$C***H***$_2$CH$_2$N), 1.57 (br, 4H, NCH$_2$C***H***$_2$C***H***$_2$CH$_2$N). ^{13}C-NMR: ***δ*** = 171.9, 171.8, 169.8, 169.7, 126.0 (q), 71.8, 70.44, 70.38, 70.3, 70.12, 70.07, 67.0, 58.9, 53.2, 50.8, 50.7, 48.1, 48.0, 37.4, 36.6, 35.0 (q), 25.6, 23.6. ^{19}F-NMR: ***δ*** = -63.9 (2t). ^{19}F-NMR (D$_2$O): ***δ*** = -64.2 (t). LC-MS: ***m/z*** = 631.9 [M+5H]$^{5+}$, 789.8 [M+4H]$^{4+}$, 1052.8 [M+3H]$^{3+}$ (calcd 3154.7 for C$_{136}$H$_{256}$F$_{12}$N$_{10}$O$_{56}$). MALDI-TOF MS: ***m/z*** = 3155.9 [M+H]$^+$, 3177.9 [M+Na]$^+$, 3193.8 [M+K]$^+$ (calcd 3154.7 for C$_{136}$H$_{256}$F$_{12}$N$_{10}$O$_{56}$). FT-IR (ATR): ***ν*** (cm^{-1}) = 3300, 2869, 1659, 1537, 1455, 1349, 1324, 1253, 1199, 1096, 947, 846, 628.

G3PPI(F$_3$-PEG)$_{16}$

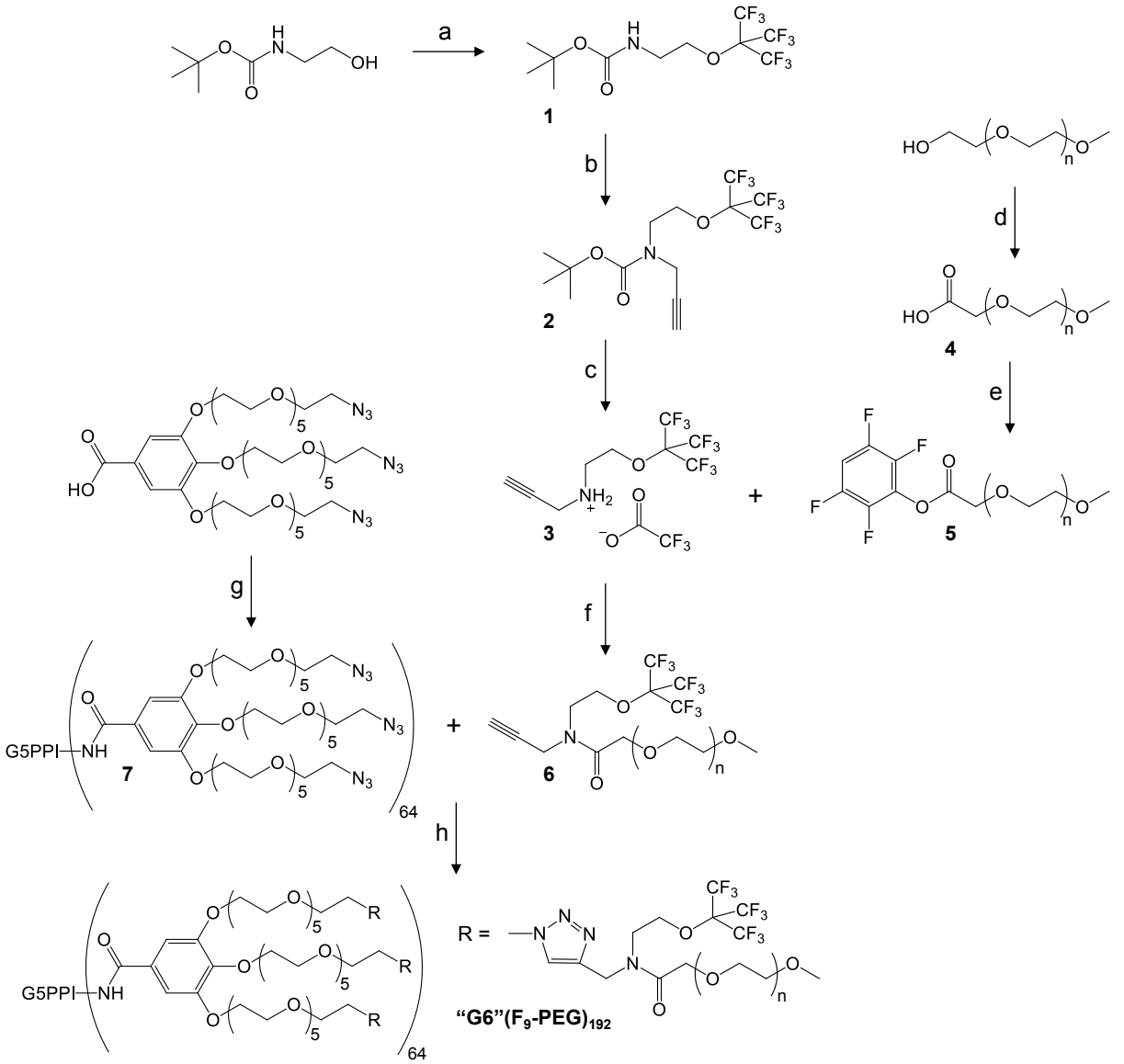


Pure **G3PPI(F$_3$-PEG)$_{16}$** was obtained as a slightly orange oil in 95% yield. ^{1}H-NMR: ***δ*** = 8.05 (br, 8H, N***H***CO), 7.92 (br, 8H, N***H***CO), 7.71 (br, 16H, N***H***CO), 4.98 (br, 8H, C***H***), 4.87 (br, 8H, C***H***), 3.77-3.52 (m, 736H,

C***H***$_2$O), 3.37 (s, 48H, C***H***$_3$), 3.24 (br, 32H, C***H***$_2$NHCO), 2.72 (br, 16H, C***H***HCF$_3$), 2.61-2.23 (br, 132H, CH***H***CF$_3$, C***H***$_2$NC***H***$_2$, C***H***$_2$CONH), 1.70-1.43 (br, 60H, NCH$_2$C***H***$_2$CH$_2$N, NCH$_2$C***H***$_2$C***H***$_2$CH$_2$N). ^{1}H-NMR (D$_2$O): ***δ*** = 4.68 (dd, 16H, C***H***), 3.84-3.61 (m, 736H, C***H***$_2$O), 3.40 (s, 48H, C***H***$_3$), 3.29 (m, 16H, C***H***$_2$NHCO), 3.18 (m, 16H, C***H***$_2$NHCO), 2.84 (m, 16H, C***H***HCF$_3$), 2.75-2.39 (m, 132H, CH***H***CF$_3$, C***H***$_2$NC***H***$_2$, C***H***$_2$CONH), 1.68 (br, 60H, NCH$_2$C***H***$_2$CH$_2$N, NCH$_2$C***H***$_2$C***H***$_2$CH$_2$N). ^{19}F-NMR: ***δ*** = -64.0 (t). ^{19}F-NMR (D$_2$O): ***δ*** = -64.0 (t). MALDI-TOF MS: ***m/z*** = 13064.6 [M+Na]$^+$ (calcd 13042.3 for $C_{568}H_{1072}F_{48}N_{46}O_{224}$). FT-IR (ATR): ***ν*** (cm^{-1}) = 3301, 2867, 1653, 1537, 1454, 1350, 1324, 1256, 1199, 1100, 1042, 948, 849, 673, 629.

S1.B. Nanoparticles with "generation 6" PPI-dendritic core: G5PPI-Gallate$(F_9\text{-PEG})_{192}$ or "G6"$(F_9\text{-PEG})_{192}$

Synthetic Procedures.



Scheme S1.2. Synthesis of the PPI 'generation 6' fluorinated dendritic nanoparticle using mPEG750 (distribution around n = 16) outer shielding groups. (a) Ph_3P, DIAD, THF, 2 h, r.t., 60 %; (b) NaH, propargyl bromide, 40 h, r.t., 59 %; (c) TFA, CH_2Cl_2, 1 h, r.t., 100 %; (d) i. NaBr, TEMPO, NaOCl, 0.25 M Na_2CO_3, 1 h, r.t. and ii. HCl, 88 %; (e) 2,3,5,6-tetrafluorophenol, pyridinium p-toluenesulfonate, EDC·HCl, CH_2Cl_2, 1 h, r.t., 100 %; (f) diisopropylethylamine, CH_2Cl_2, r.t., 17 h, 70 %; (g) G5-PPI$(NH_2)_{64}$ dendrimer, diisopropylethylamine, PyBOP, CH_2Cl_2, 4 h, r.t., 100 %; (h) $CuSO_4 \cdot 5\ H_2O$, ascorbic acid, THF / H_2O 2:1, r.t., 4 h, 50 %.

***N*-(2-(2,2,2-Trifluoro-1,1-bis(trifluoromethyl)ethoxy)ethyl)carbamic acid, 1,1-dimethylethyl ester (1)**

In a 50 mL round-bottom flask, ***N***-(2-hydroxyethyl)carbamic acid, 1,1-dimethylethyl ester (1.15 g, 7.0 mmol) and Ph_3P (3.15 g, 11.9 mmol, 1.7 eq) were dissolved in dry THF (4 mL). The mixture was put under an Ar atmosphere and cooled on an ice bath to 0 °C. Subsequently, perfluoro-***t***-butanol (1.46 mL, 10.5 mmol, 1.5 eq) and DIAD (2.06 mL, 9.9 mmol, 1.4 eq, dropwise over 20 min) were added and the solution was stirred at r.t. for 2 h. The solvent was removed ***in vacuo*** and the residue was stirred in ether (35 mL) for 10 min and stored at -20 °C for 1 h. The white solid (2.75 g) was removed by filtration, the filtrate was evaporated to dryness and the resulting oil was re-dissolved and stirred in ether (14 mL) for 10 min and stored at -20 °C for 16 h. The white solid (1.40 g) was removed by filtration, the filtrate was evaporated to dryness and the resulting oil was purified using column chromatography (flash silica: gradient pentane / CH_2Cl_2 3:1 to CH_2Cl_2). This yielded pure **1** (1.58 g, 4.2 mmol, 60 %) as a colorless oil. ^{1}H-NMR: δ = 4.83 (br, 1H, N***H***), 4.09 (t, 2H, C***H***$_2$O), 3.41 (q, 2H, NHC***H***$_2$), 1.45 (s, 9H, C***H***$_3$). ^{13}C-NMR (CD_2Cl_2): δ = 156.2, 120.8 (q), 81.2 (m), 79.9, 69.7, 40.8, 28.4. ^{19}F-NMR: δ = -70.4. GC-MS (***m/z***), single peak: Calc. for $C_{11}H_{14}F_9NO_3$ 379.08; Obs. 324 (M - ***t***-butyl), 280 (M - ***t***-Boc). FT-IR: ν (cm^{-1}) = 3318, 2981, 2942, 1706, 1682, 1540, 1480, 1470, 1446, 1429, 1413, 1394, 1368, 1245, 1148, 1115, 1082, 1028, 1005, 969, 870, 812, 787, 763, 734, 726, 647, 573, 555, 538, 504, 456.

***N*-(2-(2,2,2-Trifluoro-1,1-bis(trifluoromethyl)ethoxy)ethyl)-*N*-(2-propyn-1-yl)carbamic acid, 1,1-dimethylethyl ester (2)**

In a 25 mL 2-neck round-bottom flask, **1** (1.25 g, 3.3 mmol) was dissolved in dry THF (4 mL) under an Ar atmosphere. The solution was cooled to 0 °C on an ice bath and NaH (60 % in mineral oil, 237 mg, 5.9 mmol, 1.8 eq) was added. After stirring at r.t. for 30 min the solution was cooled to 0 °C on an ice bath and propargyl bromide (80 % in toluene, 0.64 mL, 5.9 mmol, 1.8 eq) was added. After stirring at r.t. for 40 h the reaction was quenched with H_2O (8 mL) and the mixture was divided between H_2O (80 mL) and $CHCl_3$ (40 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 40 mL) and the combined organic layers were dried with Na_2SO_4 and filtrated. After removal of the solvent ***in vacuo*** the resulting oil was purified using column chromatography (flash silica: gradient pentane / $CHCl_3$ 3:1 to $CHCl_3$). This yielded pure **2** (0.82 g, 2.0 mmol, 59 %) as a colorless oil. ^{1}H-NMR: δ = 4.24-4.02 (m, 4H, NC***H***$_2$C***H***$_2$O) 3.59 (t, 2H, C***H***$_2$C≡C), 2.22 (s, 1H, C≡C***H***), 1.47 (s, 9H, C***H***$_3$). ^{13}C-NMR: δ = 154.7, 120.5 (q), 81.0, 79.8 (m), 79.4, 72.1, 71.6, 68.9, 68.2, 46.3, 46.0, 38.3, 37.1, 28.4. ^{19}F-NMR: δ = -70.50, -70.53. All NMR spectra display the presence of two rotamers. GC-MS (***m/z***), single peak: Calc. for $C_{14}H_{16}F_9NO_3$ 417.10; Obs. 361 (M - ***t***-butyl), 316 (M - ***t***-Boc). FT-IR: ν (cm^{-1}) = 3317, 3260, 2981, 2936, 1699, 1479, 1459, 1406, 1369, 1348, 1265, 1245, 1155, 1135, 1071, 1024, 1008, 970, 861, 829, 774, 735, 726, 691, 662, 631, 571, 538, 489, 455.

***N*-(2-(2,2,2-Trifluoro-1,1-bis(trifluoromethyl)ethoxy)ethyl)-2-propyn-1-amine, 2,2,2-trifluoroacetate (1:1) (3)**

In a 50 mL round-bottom flask, **2** (0.98 g, 2.3 mmol) was dissolved in CH_2Cl_2 (5 mL). Under an Ar atmosphere, TFA (5 mL) was added and the solution was stirred at r.t. for 1 h. The solvents were removed ***in vacuo*** (oil pump, 40 °C) yielding pure **3** (1.15 g, >100 %, difficult to remove last traces of solvent) as a colorless oil. ^{1}H-NMR (5 % d_4-MeOD in $CDCl_3$): δ = 4.42 (t, 2H, C***H***$_2$O), 3.92 (d, 2H, C***H***$_2$C≡C), 3.55 (t, 2H, NHC***H***$_2$), 2.61 (t, 1H, C≡C***H***). ^{13}C-NMR (5 % d_4-MeOD in $CDCl_3$): δ = 162.4 (q), 120.1 (q), 116.7 (q), 79.6 (m), 78.1, 72.5, 65.4, 45.3, 36.7. ^{19}F-NMR (5 % d_4-MeOD in $CDCl_3$): δ = -70.4 (CC***F***$_3$), -76.2 (COC***F***$_3$). GC-MS (***m/z***), single peak: Calc. for $C_9H_8F_9NO$ 317.05; Obs. 317 (M). FT-IR: ν (cm^{-1}) = 3313, 2990, 2800, 2456, 2138, 1782, 1663, 1498, 1471, 1433, 1308, 1256, 1157, 1061, 1010, 973, 908, 839, 798, 767, 736, 726, 707, 688, 659, 597, 539, 518.

mPEG750-COOH (4)

In a 500 mL round-bottom flask, mPEG750-OH (2.0 g, 2.7 mmol), TEMPO (0.39 g, 2.4 mmol, 0.9 eq) and NaBr (0.39 g, 3.8 mmol, 1.4 eq) were dissolved in 0.25 M Na_2CO_3 (390 mL, pH = 11). Note that this commercially available mPEG750-OH building block is not monodisperse, but polydisperse. On an ice bath, NaOCl (13 mL (13 % active chorine), 27 mmol, 10 eq) was added dropwise and the solution was stirred at r.t. for 1 h. Consequently, 1 M $NaHSO_3$ (300 mL) and conc. HCl (16 mL, up to pH = 2) were added. The aqueous solution was extracted with $CHCl_3$ (3 × 140 mL), the combined organic fractions were dried with $MgSO_4$ and the solvent was removed ***in vacuo***. Trituration with hot ether (20 mL), centrifugation (5 min at 4000 rpm), decantation and removal of the solvent ***in vacuo*** yielded pure **4** (1.78 g, 2.4 mmol, 88 %) as a colorless solid. ^{1}H-NMR: δ = 4.15 (s, 2H, C***H***$_2$COOH), 3.80-3.52 (m, OC***H***$_2$), 3.38 (s, 3H, OC***H***$_3$). ^{13}C-NMR: δ = 171.7, 71.7, 70.7, 70.4, 70.3, 68.3, 58.8. ESI-MS (***m/z***): Calc. for $C_{35}H_{70}O_{19}$ (n = 16) 794.45; Obs. $[M+Na]^+$ 817.75, $[M+2Na]^{2+}$ 420.42 (mass envelopes with $\Delta m/z = 44/z$). FT-IR: ν (cm^{-1}) = 2867, 1758, 1456, 1349, 1325, 1297, 1248, 1200, 1094, 1039, 947, 849, 751, 666, 527.

mPEG750-COOTFP (5)

In a 50 mL round-bottom flask, **4** (1.47 g, 2.0 mmol), 2,3,5,6-tetrafluorophenol (0.37 g, 2.2 mmol, 1.1 eq) and pyridinium ***p***-toluenesulfonate (49 mg, 0.19 mmol, 0.1 eq) were dissolved in CH_2Cl_2 (5 mL). EDC·HCl (0.42 g, 2.1 mmol, 1.1 eq) was added and the solution was stirred at r.t. for 1 h. $CHCl_3$ (90 mL) was added and the solution was washed with $NaHCO_{3\,(sat)}$ and brine (both 25 mL). The organic layer was dried with $MgSO_4$, filtrated and the solvent was removed ***in vacuo***. This yielded pure **5** (1.87 g, >100 %, difficult to remove last traces of solvent) as a colorless oil, which was used immediately without further purification. ^{1}H-NMR: δ = 7.03 (m, 1H, Ar***H***), 4.56 (s, 2H, C***H***$_2$COO), 3.85-3.53 (m, OC***H***$_2$), 3.38 (s, 3H, OC***H***$_3$). ^{19}F-NMR: δ = -138.6, -152.7.

mPEG750(^{19}F)-≡ (6)

In a 50 mL round-bottom flask, **3** (0.85 g, 2.0 mmol) was dissolved in CH_2Cl_2 (2 mL) and diisopropylethylamine (2.1 mL, 12 mmol, 6 eq). Under an Ar atmosphere, **5** (1.76 g, 2.0 mmol, 1 eq) was added and the solution was stirred at r.t. for 17 h. $CHCl_3$ (120 mL) was added and the organic layer was washed with $NaHCO_{3\,(sat)}$, 0.1 M HCl and brine (all 50 mL), dried (Na_2SO_4), filtrated and the solvent was removed ***in vacuo***. Column chromatography (flash silica: gradient $CHCl_3$ to 8 % MeOH in $CHCl_3$) yielded impure product. Purification was achieved by dissolving in 0.1 M NaOH (100 mL) and brine (25 mL) and extraction with $CHCl_3$ (3 × 40 mL). After drying (Na_2SO_4), filtration and removal of the solvent ***in vacuo*** this yielded pure **6** (1.44 g, 1.4 mmol, 70 %) as a beige waxy solid. ^{1}H-NMR: $\boldsymbol{\delta}$ = 4.29 (s, 2H, NCOC***H***$_2$), 4.28-4.17 (m, 4H, NC***H***$_2$C***H***$_2$O) 3.90-3.48 (m, OC***H***$_2$, C***H***$_2$C≡C), 2.32 & 2.25 (2t, 1H, C≡C***H***). ^{13}C-NMR: $\boldsymbol{\delta}$ = 169.3, 169.1, 120.0 (q), 79.6 (m), 78.0, 77.8, 73.0, 72.6, 71.7, 70.34, 70.27, 70.2, 70.1, 70.0, 68.3, 67.9, 58.7, 46.0, 45.4, 38.8, 38.1, 34.5. ^{19}F-NMR: $\boldsymbol{\delta}$ = -70.3, -70.5. All NMR spectra display the presence of two rotamers. ESI-MS (***m/z***): Calc. for $C_{42}H_{72}F_9NO_{18}$ (n = 16) 1049.46; Obs. $[M+Na]^+$ 1072.42, $[M+2Na]^{2+}$ 547.83 (mass envelopes with $\Delta m/z = 44/z$). FT-IR: $\boldsymbol{\upsilon}$ (cm^{-1}) = 3242, 2869, 1661, 1460, 1349, 1267, 1249, 1095, 1019, 971, 851, 802, 766, 734, 727, 538.

G5PPI-Gallate(HEG-N$_3$)$_{192}$ (7)

In a 10 mL round-bottom flask, G5-PPI(NH_2)$_{64}$ (20.9 mg, 2.9 μmol) and 3,4,5-tris((17-azido-3,6,9,12,15-pentaoxaheptadec-1-yl)oxy) benzoic acid (232 mg, 0.22 mmol, 1.2 eq per NH_2) were dissolved in CH_2Cl_2 (1½ mL). Diisopropylethylamine (120 μL, 0.68 mmol, 3 eq to the benzoic acid derivative) and PyBOP (119 mg, 0.22 mmol, 1.2 eq per NH_2) were added and the mixture was stirred at room temperature for 4 h. $CHCl_3$ (60 mL) was added and the solution was washed with 0.1 M NaOH (20 mL), dried with Na_2SO_4 and filtrated. Removal of the solvent ***in vacuo*** followed by BioBeads SX-1 (10 % MeOH in $CHCl_3$) yielded pure 7 (210 mg, 2.9 μmol, 100 %) as a yellowish solid. ^{1}H-NMR: $\boldsymbol{\delta}$ = 8.16 (br, 64H, N***H***), 7.08 (br, 128H, Ar***H***), 4.08 (br, 128H, ArOC***H***$_2$), 3.92 (br, 256H, ArOC***H***$_2$), 3.80-3.40 (m, 3840H, OC***H***$_2$), 3.40-3.30 (m, 512H, C***H***$_2$N$_3$, C***H***$_2$NHCO), 2.44 (br, 372H, NC***H***$_2$), 1.95-1.45 (br, 252H, NCH$_2$C***H***$_2$). ^{13}C-NMR: $\boldsymbol{\delta}$ = 167.1, 152.2, 140.7, 129.6, 106.6, 73.4, 72.3, 71.4, 70.52, 70.45, 70.0, 69.5, 68.7, 67.7, 51.3, 50.61, 50.58, 50.0, 38.6, 27.4, 24.7. FT-IR: $\boldsymbol{\upsilon}$ (cm^{-1}) = 3334, 2867, 2099, 1636, 1580, 1542, 1496, 1453, 1425, 1332, 1287, 1243, 1098, 944, 850, 760, 732, 699, 665, 646, 557, 505. FT-IR shows a very strong and specific signal for the azide groups at $\boldsymbol{\upsilon}$ = 2099 cm^{-1}. The calculated molecular weight for this dendritic core molecule is 72,455 kDa ($C_{3128}H_{5552}N_{702}O_{1216}$).

G5PPI-Gallate(F$_9$-PEG)$_{192}$ or "G6"-(F$_9$-PEG)$_{192}$

In a 25 mL round-bottom flask, 7 (97 mg, 1.3 μmol, 0.26 mmol N_3) and **6** (284 mg, 0.27 mmol, 1.05 eq) were dissolved in THF (5 mL). Under an Ar flow, solvent was removed until ~4 mL THF remained. Ascorbic acid (0.65 mL of a fresh 0.08 M solution in H_2O, 52 μmol, 0.2 eq) and $CuSO_4 \cdot 5H_2O$ (0.65 mL of a fresh 0.04 M

solution in H_2O, 26 μmol, 0.1 eq) were added and the solution was stirred at r.t. for 4 h. $CHCl_3$ (100 mL) was added and the mixture was divided between $CHCl_3$ and 1:1 brine / 0.1 M NaOH (40 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 15 mL) and the combined organic layers were dried (Na_2SO_4), filtrated and the solvent was removed ***in vacuo***. To remove any remaining copper ions, the residue was dissolved in $HCl_{(aq)}$ (12 mL, pH = 4) and stirred with DOWEX 50WX8 (H-form, 1.0 g) at r.t. for 45 min. After filtration and washing with $HCl_{(aq)}$ (pH = 4, 2 × 15 mL), 0.1 M NaOH (~ 100 mL) and brine (50 mL) were added (to pH > 11) and the aqueous phase was extracted with $CHCl_3$ (3 × 50 mL). The combined organic fractions were dried with Na_2SO_4, filtrated and the solvent was removed ***in vacuo***. BioBeads SX-1 (10 % MeOH in $CHCl_3$) yielded pure "**G6**"(**F**$_9$-**PEG**)$_{192}$ (190 mg, 0.67 μmol, 50 %) as an orange oil. ^{1}H-NMR: $\boldsymbol{\delta}$ = 7.72 (s, 192H, triazole-***H***), 7.12 (br, 128 H, Ar***H***), 4.68-4.16 (m, 1920H, NCOC***H***$_2$, NC***H***$_2$C***H***$_2$O, CC***H***$_2$N, C***H***$_2$NN=N), 3.91-3.41 (m, OC***H***$_2$), 3.38 (s, 576H, OC***H***$_3$). Due to the broadness of the ^{1}H NMR spectrum, various resonances overlap and cannot be observed separately. ^{19}F-NMR: $\boldsymbol{\delta}$ = - 70.39 (m). All NMR spectra display the presence of rotamers. FT-IR: $\boldsymbol{\upsilon}$ (cm^{-1}) = 3525, 3347, 2868, 1673, 1581, 1535, 1490, 1457, 1348, 1331, 1295, 1247, 1200, 1097, 1048, 948, 849, 765, 718, 656, 556. Note that the resonance at 2099 cm^{-1} of the azide groups of reactant **7** has disappeared. Complete modification of the azide groups in **7** with alkyn **6** gives an average molecular weight of 282.5 kDa for this nanoparticle construct "**G6**"(**F**$_9$-**PEG**)$_{192}$.

Nanoparticle	**G1PPI(F_3-PEG)$_4$**	**G3PPI(F_3-PEG)$_{16}$**	**G5PPI(F_3-PEG)$_{64}$**	**"G6"(F_9-PEG)$_{192}$**
Type of dendritic core	G1PPI-$(NH_2)_4$	G3PPI-$(NH_2)_{16}$	G5PPI-$(NH_2)_{64}$	G5PPI-Gallate-$(HEG\text{-}N_3)_{192}$
Number of exterior mPEG groups	4	16	64	192
Type of coronal shielding group	mPEG-543 (discrete $\boldsymbol{M}_w$)	mPEG-543 (discrete $\boldsymbol{M}_w$)	mPEG-543 (discrete $\boldsymbol{M}_w$)	mPEG-750 (distribution in $\boldsymbol{M}_w$)
Type of ^{19}F group	$-CF_3$	$-CF_3$	$-CF_3$	$-C(CF_3)_3$
wt% ^{19}F	7.2	7.0	6.9	11.6
Molecular weight (kDa)	3.158	13.043	52.592	282.500
Hydrodynamic diameter ($\boldsymbol{d}_h$)	3.4±0.3	4.6±0.2	7.5±0.3	11.0±0.5
$\boldsymbol{T}_1$ (ms) of PEG-^1H at 7.0 T	633±20	538±18	529±23	432±33
$\boldsymbol{T}_2$ (ms) of PEG-^1H at 7.0 T	589±25	505±28	375±30	294±28
$\boldsymbol{T}_1$ (ms) of ^{19}F labels at 7.0 T	620±12	561±11	412±15	543±24
$\boldsymbol{T}_2$ (ms) of ^{19}F labels at 7.0 T	400±10	240±12	129±12	82±7

Table S1.1. Overview of the features and physical properties of the four different ^{19}F labeled nanoparticles. The hydrodynamic diameters of the **G1PPI(F_3-PEG)$_4$** and **G5PPI(F_3-PEG)$_{64}$** nanoparticles deviate slightly from those in ref [2], as the numerous diffusion measurements in this work led to more reliable estimates.

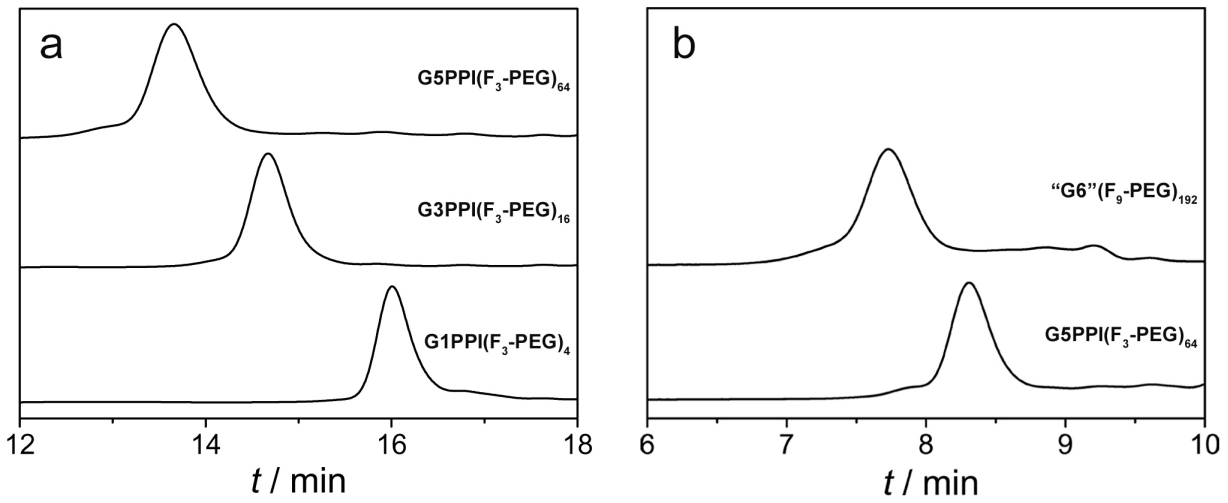


Figure S1.1. Gel permeation chromatography (GPC) on (a) nanoparticles **G1PPI(F_3-PEG)$_4$**, **G3PPI(F_3-PEG)$_{16}$**, **G5PPI(F_3-PEG)$_{64}$** in aqueous solution and (b) nanoparticles **G5PPI(F_3-PEG)$_{64}$** and **"G6"(F_9-PEG)$_{192}$** in DMF/LiBr. These chromatograms clearly show the increase in hydrodynamic volume upon increasing the dendrimer size.

S2. Relaxation times of poly(ethylene glycol) solutions in water

Kuhn length b

$b = C_\infty l/\cos(\theta/2)$, where C_∞ = 5.5 (Flory characteristic ratio)[3], l = 0.146 nm (average bond length in $(C–C–O–)_n$ backbone)[4], θ = 70° (average backbone bond angle)[4], so Kuhn length $b \cong$ 0.98 nm.

Kuhn monomer relaxation time τ_0

$$\tau_0 \cong \frac{\eta_s b^3}{k_B T}$$

η_s = 1 mPa s (viscosity of water at room temperature), $b \cong$ 0.98 nm (PEG Kuhn length), k_B the Boltzmann constant, T = 293 K (room temperature), so $\tau_0 \cong$ 0.2 ns.

Kuhn monomers per entanglement strand in the melt $N_e(1)$

$N_e(1) = (a(1)/b)^2$, where $a(1)$ = 3.73 nm (tube diameter in the melt)[5] and $b \cong$ 0.98 nm (Kuhn length), so $N_e(1) \cong$ 14.

Reptation time τ_{rep}

$$\tau_{rep} \cong \tau_0 \frac{N^3}{N_e(1)} \phi^{3(1-\nu)/(3\nu-1)} \cong \tau_0 \frac{N^3}{N_e(1)} \phi^{3/2} \quad (\nu = 3/5 \text{ in good solvent})$$

$N_e(1)$ = 14 (monomers per entanglement in the melt), $\phi \cong$ 0.60 (highest polymer volume fraction used in this study), $M_0 = M_e/N_e = 2000/14 = 1.4\times10^2$ g/mol (Kuhn monomer molar mass)[5], so N(6 kDa) = $6\times10^3/1.4\times10^2$ = 43, N(20 kDa) = $20\times10^3/1.4\times10^2 = 1.4\times10^2$, N(35 kDa) = $35\times10^3/1.4\times10^2 = 2.5\times10^2$ and N(100 kDa) = $100\times10^3/1.4\times10^2 = 7.0\times10^2$ (number of Kuhn monomers per chain). Conclusion: τ_{rep}(6 kDa) $\cong$ 0.5 µs, τ_{rep}(20 kDa) $\cong$ 0.02 ms, τ_{rep}(35 kDa) $\cong$ 0.1 ms and τ_{rep}(100 kDa) $\cong$ 2 ms.

In the case of 6 kDa PEG, the number of entanglements formed per strand is N(6 kDa)$/N_e(1)$ =43/14 =3. Because this number is $\ll$ 10, PEG 6 kDa cannot be considered to entangle.

For PEG weights up to 100 kDa, the slowest dynamical process is apparently still faster than 10 ms, which is the onset of the NMR diffusometry time scale. We therefore measure terminal self-diffusion coefficients at the experimental time scale (100 ms) even in case the entanglements would influence particle self-diffusion.

S3. Length scales in solutions of poly(ethylene glycol) in water

Overlap concentration, correlation length, radius of gyration

Chain overlap concentration ϕ^* is given by $\phi^* = \frac{M_W}{\frac{4}{3}\pi\left(R_g^{\phi^*}\right)^3 \rho N_A}$ (in g/m^3), where $\boldsymbol{M}$ is molecular weight, $R_g^{\phi^*} = 0.215\times10^{-10} M_w^{7/12}$ (radius of gyration at the overlap concentration: $R_g^{\phi^*}$(6 kDa) = 3.4 nm, $R_g^{\phi^*}$(20 kDa) = 6.9 nm, $R_g^{\phi^*}$(35 kDa) = 9.6 nm and $R_g^{\phi^*}$(100 kDa) = 18 nm)[6], ρ = 1081 kg/m^3 (density)[5] and N_A Avogadro's number (mol^{-1}). This results in ϕ^*(6 kDa) = 0.054, ϕ^*(20 kDa) = 0.022, ϕ^*(35 kDa) = 0.014 and ϕ^*(100 kDa) = 0.0066.

Above the overlap concentration, correlation length/blob size decreases as $\xi(\phi) = R_g^{\phi^*}\left(\frac{\phi}{\phi^*}\right)^{-3/4}$ while the radius of gyration decreases as $R_g(\phi) = R_g^{\phi^*}\left(\frac{\phi}{\phi^*}\right)^{-1/8}$.

Entanglement volume fraction, tube diameter

Entanglement volume fraction $\phi_e = \left(\frac{N_e(1)}{N}\right)^{3/4}$. N is the number of Kuhn monomers per chain ($\boldsymbol{N}$(6 kDa) = 43, $\boldsymbol{N}$(20 kDa) =1.4×10^2, $\boldsymbol{N}$(35 kDa) = 2.5×10^2 and $\boldsymbol{N}$(100 kDa) = 7.0×10^2, cf. S2). The number of entanglements per entanglement strand in the melt $N_e(1)$ = 14 (cf. S2). PEG 6 kDa will therefore never truly entangle. This results in ϕ_e(20 kDa) = 0.17, ϕ_e(35 kDa) = 0.11 and ϕ_e(100 kDa) = 0.051.

Above the entanglement concentration, tube diameter $a(\phi) = a(1)\phi^{-3/4}$, where the tube diameter in the melt $a(1)$ = 3.73 nm.[5]

S4. Macroscopic zero-shear viscosities η_m of poly(ethylene glycol) solutions in water at different polymer volume fractions

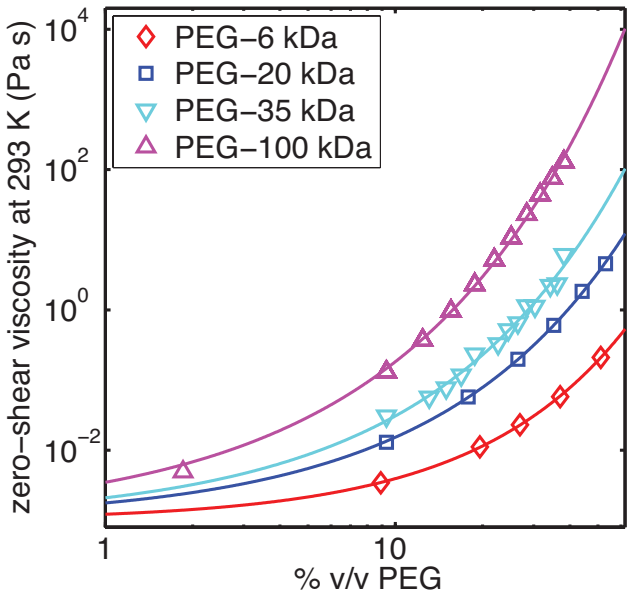


Figure S4.1. Macroscopic zero-shear viscosities η_m of PEG solutions as a function of volume fraction. The data points were fitted with stretched exponential functions with the condition that the viscosity of a 0% v/v solution has the viscosity of water at 293 K (1 mPa s).

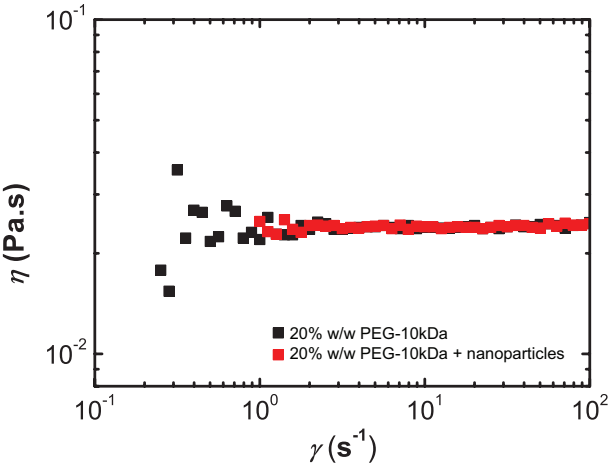


Figure S4.2. Example of the effect of addition of nanoparticles on bulk solution viscosity. The addition of nanoparticles (d_h= 4.6 nm, 0.1 % w/w) does not lead to a significant change of the flow curve of a PEG solution at a concentration of 20% w/w.

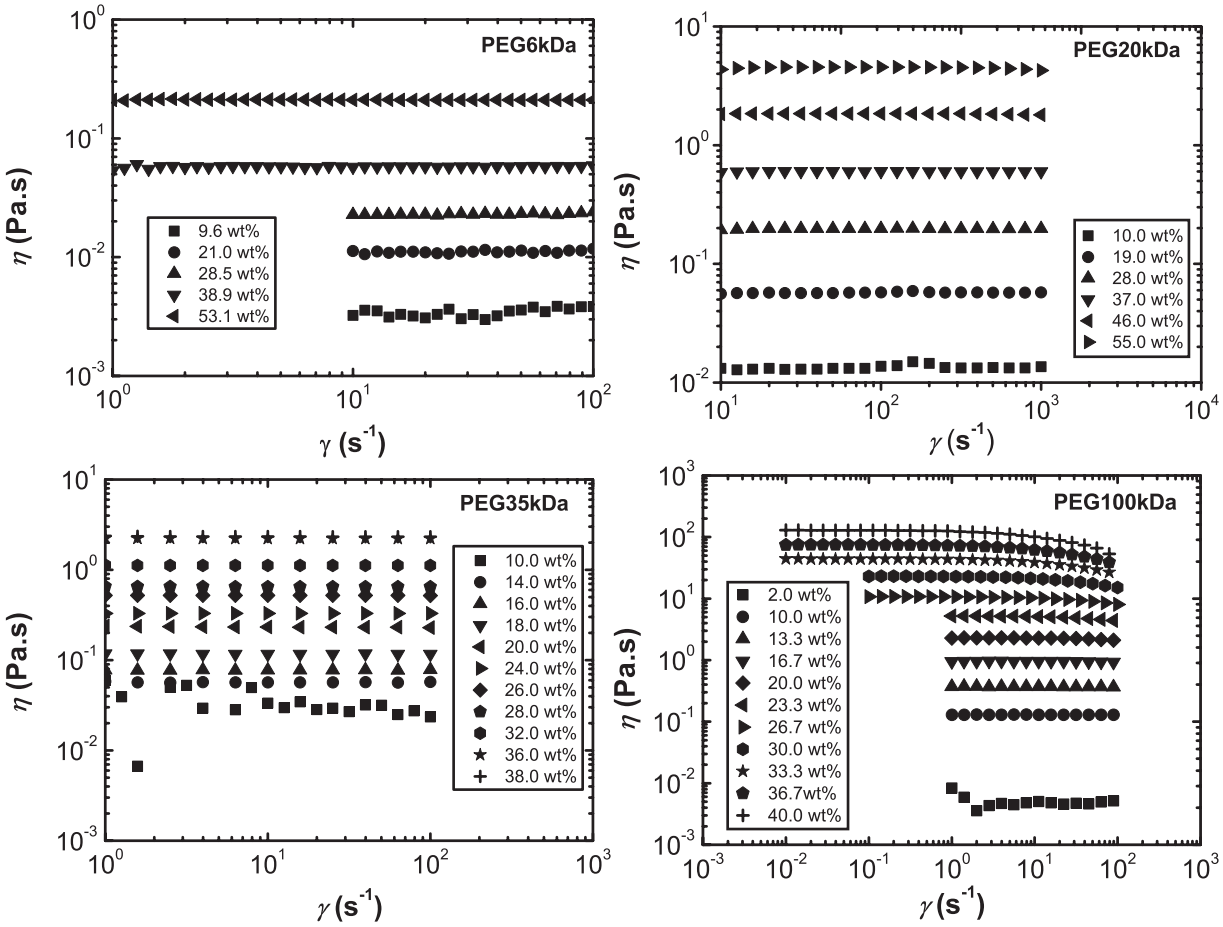


Figure S4.3. Flow curves underlying Figure 4.1. Shear thinning behavior was only observed for PEG-100kDa in the measured shear rate domain. The viscosities in Figure 4.1 are the plateau values.

S5. Ratio $D/D(\eta_m)$ for all data points

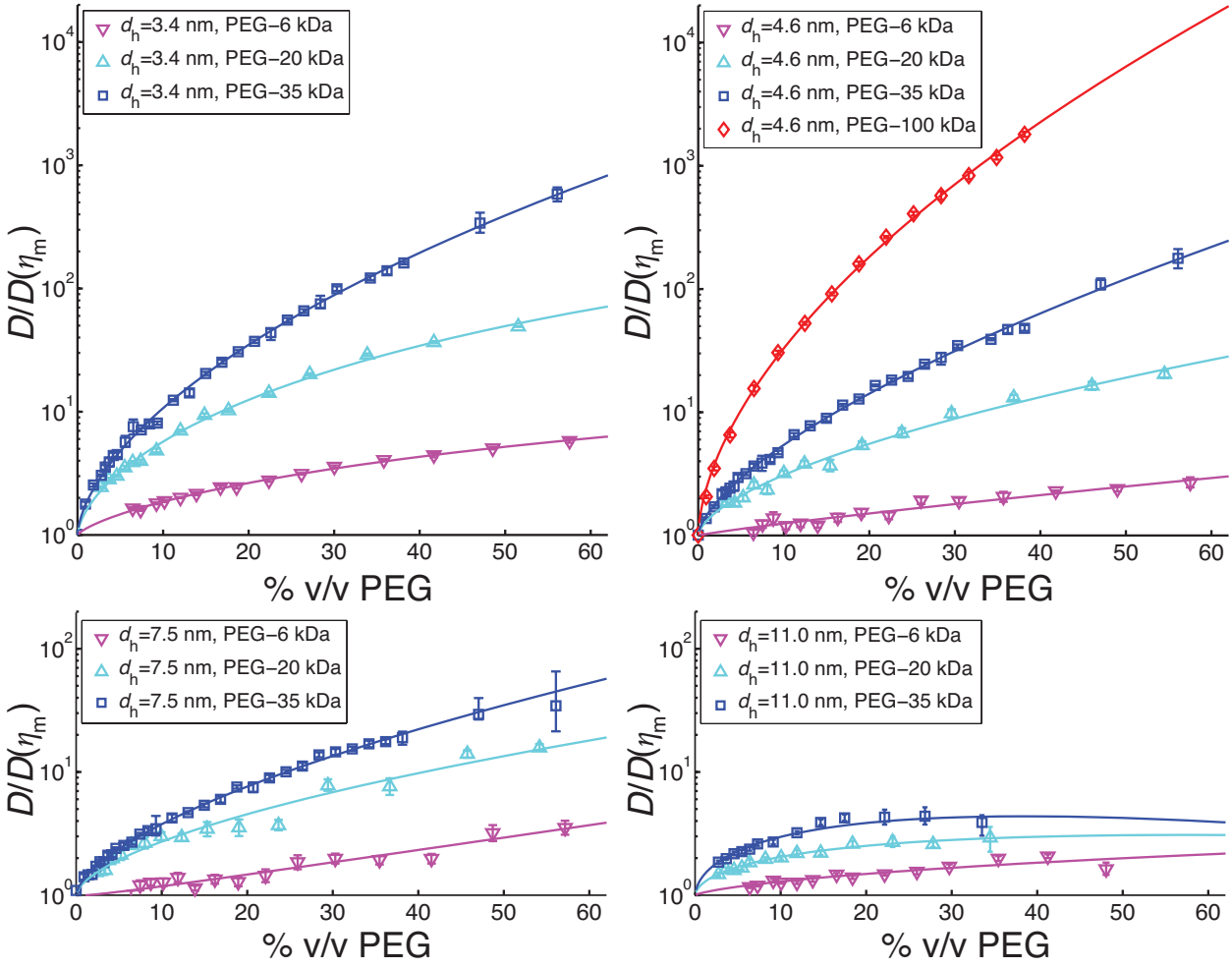


Figure S5.1. $D/D(\eta_m)$ ratio for all data points, where $D(\eta_m)$ follows from the Stokes-Einstein relation.

S6. Plots of (D/D_0) against R_g/ξ and d/ξ for all data points

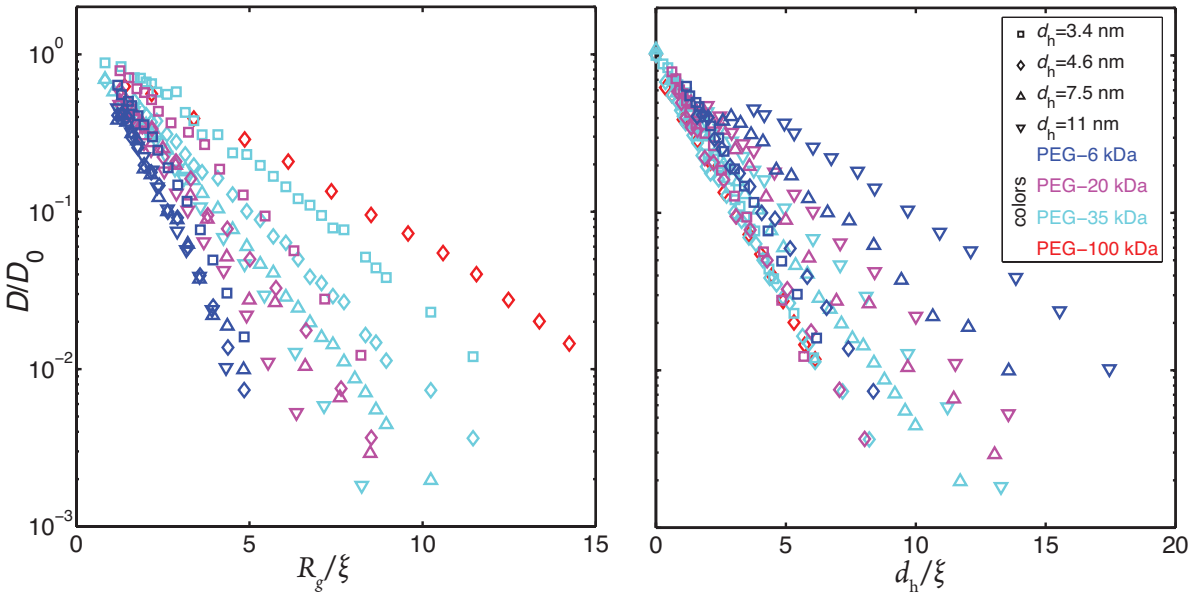


Figure S6.1. Plots of (D/D_0) against R_g/ξ and d/ξ for all data points. Here, $\xi(\phi) = R_g^{\phi^*}\left(\frac{\phi}{\phi^*}\right)^{-3/4}$ and $R_g(\phi) = R_g^{\phi^*}\left(\frac{\phi}{\phi^*}\right)^{-1/8}$, where ϕ is polymer volume fraction.

S7. Effect of normalization to $\varphi_{\xi=d}$ at both $d > R_g$ and $d < R_g$

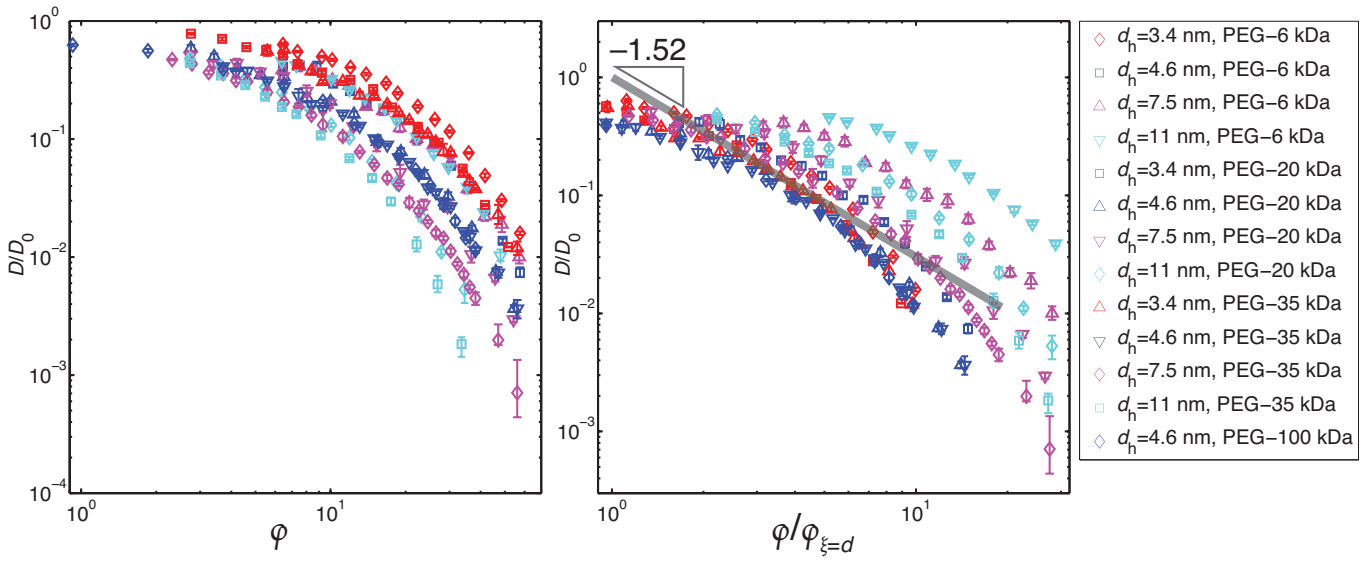


Figure S7.1. In this figure, the effect of normalization of the data points to the crossover point into the intermediate regime $\varphi_{\xi=d}$ is shown. For particles larger than $R_g^{\phi^*}$ (the polymer coil size at the overlap concentration), we use a trivial backprediction of ξ to calculate an "apparent" $\varphi_{\xi=d}$. Careful comparison of the left and right panels leads to the conclusion that this normalization leads to overlap of those data points belonging to intermediate particles smaller than the polymer coil size only ($\xi < d < a$ and $d < R_g$). Only these points are shown in Figure 8 in the main text.

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