

## Supporting Information

### Synthesis of Fluorine-18 Functionalized Nanoparticles for use as *in vivo* Molecular Imaging Agents

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#### General Information.

NMR spectra were measured in CDCl<sub>3</sub> or DMSO-d<sub>6</sub> on Varian Mercury 300 MHz spectrometers unless otherwise noted. <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts are reported in ppm relative to CDCl<sub>3</sub> (δ=7.27). Flash column chromatography of organic compounds was performed using silica gel 60 (230-400 mesh).

High-resolution mass spectra (EI and FAB) were provided by California Institute of Technology Mass Spectrometry Facility.

DLS instrumentation consisted of a Brookhaven Instruments Limited (Holtsville, NY) system, including a model BI-200SM goniometer, a model BI-9000AT digital correlator, a model HC120-08 photomultiplier, and a laser operated at 659 nm. Measurements were made at 25 °C. Prior to analysis, solutions were centrifuged in a Beckman model TJ-6 centrifuge at 2000 rpm for 5 min to sediment dust particles. Scattered light was collected at a fixed angle of 90°. The digital correlator was operated with 250 ratio spaced channels, an initial delay of 5 μs, a final delay of 50 ms, and a duration of 10 min. The calculations of the particle size distributions and distribution averages were performed with the ISDA software package (Brookhaven Instruments Company), using CONTIN particle size distribution analysis routines. All measurements were made in triplicate.

AFM images were taken using a Nanoscope IV Scanning Probe Microscope Controller (Digital Instruments, Veeco Metrology Group) in tapping mode in air at room

temperature using Veeco model TESP tips (spring constant = 20-80 N/m, resonance frequency = 297-335 kHz). The samples were prepared by drop coating onto silicon 111 surfaces that had been prepared by immersion for 5 minutes at 55 °C in a solution of H<sub>2</sub>O/NH<sub>4</sub>OH(30% in H<sub>2</sub>O)/H<sub>2</sub>O<sub>2</sub>(50% in H<sub>2</sub>O) (5:1:1) followed by washing with DI water and drying with compressed air. Samples were drop coated onto the substrates, and excess solvent was removed by wicking with filter paper.

Photoreactions were done using a 450 W medium pressure mercury arc lamp (Ace Glass). Reactions were done using a water cooled quartz jacket surrounding the lamp immersed in the reaction mixture.

Gel permeation chromatography (GPC) was carried out in DMF on two I-series MBLMW ViscoGel columns (Viscotek) connected in series with a DAWN EOS multiangle laser light scattering (MALLS) detector and an Optilab DSP differential refractometer (both from Wyatt Technology). No calibration standards were used, and dn/dc values were obtained for each injection by assuming 100% mass elution from the columns.

UV-Vis spectra were taken on a Beckman DU 7400 spectrophotometer.

**Materials.** CH<sub>2</sub>Cl<sub>2</sub> and THF were purified by passage through solvent purification columns.<sup>1</sup> (H<sub>2</sub>IMes)(pyr)<sub>2</sub>(Cl)<sub>2</sub>Ru=CHPh (**6**) was prepared from (H<sub>2</sub>IMes)(PCy<sub>3</sub>)(Cl)<sub>2</sub>Ru=CHPh which was obtained from Materia according to a literature procedure.<sup>2</sup> Aminohydroxy(poly ethylene glycol) was made according to a literature procedure.<sup>3</sup> Cis-5-norbornene-endo-2,3-dicarboxylic anhydride was purchased

from Acros Organics. All other commercially available materials were obtained from Aldrich Chemical Company and used as received unless otherwise noted.

**Cis-5-norbornene-exo-2,3-dicarboxylic anhydride (1).**

A round-bottom flask was charged with cis-5-norbornene-endo-2,3-dicarboxylic anhydride (198 g). 200 mL 1,2-dichlorobenzene was added, a condenser was attached, and the reaction apparatus was immersed in an oil bath at 185 °C for 4 h. Once cool, the flask was further cooled to 0 °C, and the precipitate was recovered by filtration and washed with hexanes. This crude product was recrystallized from benzene six times to yield 31 g pure exo product (16% yield). <sup>1</sup>H NMR: δ 1.42-1.47 (m, 1H), 1.51 (dt, J = 10.2, 1.5 Hz, 1H), 3.01 (d, J = 1.5 Hz, 2H), 3.44-3.47 (m, 2H), 6.34 (t, J = 1.8 Hz, 2H). <sup>13</sup>C NMR: δ 171.78, 138.14, 48.95, 47.06, 44.30. HRMS: calculated 164.0474, found 164.0468.

**N-(hydroxyethyl)-cis-5-norbornene-exo-2,3-dicarboximide (2).**

A round-bottom flask was charged with anhydride **1** (2.07g, 1 eq.). To the flask was added 15 mL toluene, followed by 2-aminoethanol (800μL, 1.05 eq.) and triethylamine (200μL, 0.11 eq.). Stirring caused insoluble clumps to form. A Dean-Stark trap was attached to the flask, and the reaction mixture was heated at reflux for 8 h. Once complete consumption of **1** was observed by TLC, the reaction mixture was concentrated *in vacuo* to yield an off-white solid. This residue was dissolved in 40 mL CH<sub>2</sub>Cl<sub>2</sub> and washed with 0.1N HCl (10 mL) and brine (10 mL). The organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo* to yield **2** as a white solid in 93% yield. <sup>1</sup>H NMR: δ

1.34 (d, J = 9.9 Hz, 1H), 1.51 (dt, J = 9.9, 1.4 Hz, 1H), 2.3 (s, 1H), 2.71 (d, J = 1.5 Hz, 2H), 3.28 (t, J = 1.5 Hz, 2H), 3.67-3.71 (m, 2H), 3.75-3.79 (m, 2H), 6.29 (t, J = 1.8 Hz, 2H). <sup>13</sup>C NMR: δ 178.95, 138.00, 60.56, 48.07, 45.45, 42.97, 41.49. HRMS: calculated 208.0974, found 208.0984.

**N-(cinnamoyl ethyl)-cis-5-norbornene-exo-2,3-dicarboximide (3).**

To a 3-necked, round-bottom flask, equipped with a stirbar, a septum, a stopper and gas inlet, was added alcohol **2** (1.022 g, 1 eq) under argon flow. 10 mL CH<sub>2</sub>Cl<sub>2</sub> was added, followed by N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.411 g, 1.49 eq) and 4-dimethylaminopyridine (60 mg, 0.10 eq). Trans-cinnamic acid (.886 g, 1.21 eq) was added as a solution in 10 mL CH<sub>2</sub>Cl<sub>2</sub> via syringe. The reaction mixture was allowed to stir under argon at room temperature for 7 h, at which point complete consumption of **2** was observed by TLC. The reaction mixture was washed with water (2x 20 mL) and dried over MgSO<sub>4</sub>. The pale yellow residue was purified by silica gel chromatography (3:2 hexanes/EtOAc) to yield **3** as a clear oil which solidified into a white solid over several days in 91% yield. <sup>1</sup>H NMR: δ 1.32 (d, J = 9.9 Hz, 1H), 1.49 (dt, J = 9.9, 1.5 Hz, 1H), 2.72 (d, J = 1.2, 2H), 3.28 (t, J = 1.8 Hz, 2H), 3.83-3.87 (m, 2H), 4.34-4.38 (m, 2H), 6.28 (t, J = 1.8 Hz, 2H), 6.36 (d, J = 16.2 Hz, 1H), 7.37-7.50 (m, 5H), 7.64 (d, J = 15.9 Hz, 1H). <sup>13</sup>C NMR: δ 178.00, 166.61, 151.02, 145.69, 137.98, 134.40, 130.63, 129.08, 128.35, 117.49, 61.08, 48.02, 45.44, 42.85, 37.76. HRMS: calculated 338.1392, found 338.1381.

**N-(hydroxy poly(ethylene glycol))-cis-5-norbornene-exo-2,3-dicarboximide (4).**

A round-bottom flask was charged with aminohydroxyPEG (1.428 g, 1 eq.) and 30 mL toluene, followed by anhydride **1** (exo anhydride) (367 mg, 1.07 equiv) and triethylamine (40  $\mu$ L, 0.1 equiv). A Dean-Stark trap was attached, and the reaction mixture was heated at reflux for 19 h, at which point complete consumption of aminohydroxyPEG was observed by TLC. The reaction mixture was concentrated *in vacuo*, and the residue was taken up in  $\text{CH}_2\text{Cl}_2$ , washed with 0.1 N HCl and brine and dried over  $\text{MgSO}_4$ . The crude product was purified by silica gel chromatography (5% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to yield **4** as a clear oil in 80% yield.  $^1\text{H}$  NMR:  $\delta$  1.35 (d,  $J = 9.9$  Hz, 1H), 1.49 (dt,  $J = 9.9$  Hz, 1.5 Hz, 1H), 2.67 (s, 2H), 3.26 (m, 2H), 3.56-3.73 (m, 50H), 6.27 (t,  $J = 1.8$  Hz, 2H).  $^{13}\text{C}$  NMR:  $\delta$  178.21, 138.00, 130.92, 70.72, 70.44, 70.01, 67.05, 61.87, 47.99, 45.44, 42.89, 37.88.

**N-(mesyl poly(ethylene glycol))-cis-5-norbornene-exo-2,3-dicarboximide (5).**

A round-bottom flask was charged with **4** (468 mg, 1 eq.) under an atmosphere of argon.  $\text{CH}_2\text{Cl}_2$  (6 mL) was added, followed by  $\text{NEt}_3$  (175  $\mu$ L, 2.0 eq.) and the reaction mixture was cooled to  $-35$   $^\circ\text{C}$ .  $\text{MsCl}$  (73  $\mu$ L, 1.5 eq.) as a solution in 2 mL  $\text{CH}_2\text{Cl}_2$  was added dropwise using a syringe pump at a rate of 0.05 mL/min. After complete addition, the reaction mixture was allowed to slowly warm to room temp. After 6 h complete consumption of **4** was observed by TLC, and the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL) and washed with 0.1 N HCl (10 mL) and brine (10 mL), then dried over  $\text{MgSO}_4$ . The crude product was purified by silica gel chromatography (5% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to yield **5** as a clear oil in 83% yield.  $^1\text{H}$  NMR:  $\delta$  1.34 (d,  $J = 9.9$  Hz, 1H), 1.49 (dt,  $J = 9.9$  Hz, 1.5 Hz, 1H), 2.68 (s, 2H), 3.08 (s, 3H), 3.26 (m, 2H), 3.56-3.72 (m, 50H),

3.73 (m, 2H), 4.38 (m, 2H) 6.28 (t, J = 1.8 Hz, 2H). <sup>13</sup>C NMR: δ 178.19, 138.01, 70.74, 70.03, 69.49, 69.20, 67.06, 47.99, 45.45, 42.90, 37.92.

### **Polymerization Procedure**

In a typical polymerization, a vial was charged with hydrophobic norbornene **3** (2.9 mg) and a stirbar under argon flow. THF (0.2 mL) was added to the vial. The desired amount of catalyst **6** as a stock solution in THF (2.5 mg/mL) was then injected into the vial. The reaction was allowed to proceed at room temperature under argon flow for 1-2 minutes, then hydrophilic norbornene **5** (21.2 mg) was added as a solution in THF (0.2 mL). All reactions were quenched by addition of ethyl vinyl ether (0.2 mL) that had been purified by passage through a short column of silica gel. The reaction mixture was allowed to stir for an additional 15 minutes before precipitation into 20 mL Et<sub>2</sub>O/hexanes (1:1). The products were recovered in 87-99% yield by decanting off the supernatant and scraping the gooey solids off of the sides of the beaker. <sup>1</sup>H NMR δ 1.30-1.70 (br s), 1.95 (s), 1.85-2.55 (br s), 2.90-3.05 (br s), 3.07 (s), 3.63 (br s), 3.75 (m), 4.36 (m), 5.38-5.80 (br m), 6.32-6.44 (br d), 7.30-7.55 (br d), 7.58-7.70 (m).

### **Micelle Formation Procedure**

Block copolymer (10mg) was dissolved in filtered (0.02 μm) THF (5 mL). Once homogeneous, filtered (0.02 μm) DI water (5 mL) was added dropwise over 10 minutes. The micelle solution was then transferred to dialysis tubing (8000 MWCO) and dialyzed against water for 24-48 hours while protected from light.

### **Micelle Crosslinking Procedure**

A photochemical reactor was charged with cloudy, aqueous micelle solution (8 mL). The solution was degassed by bubbling with argon for 20 minutes. A UV lamp (450 W medium pressure) was inserted into the photochemical reactor, and the solution was irradiated for 3 minutes. Samples were lyophilized while protected from light before use in radiofluorination reactions.

### **Radiofluorination Procedure**

A 5 mL reaction vessel in a fume hood with a leaded glass sash was charged with hydrated  $K^{18}F$  (361 mCi).  $K_2CO_3$  (1 mg) and kryptofix 222 (10 mg) in 1 mL acetonitrile were added to the vessel. The solvent was boiled off by submersing the vessel in an oil bath at 120 °C while bubbling  $N_2$  through the reaction mixture. BHT in dry acetonitrile (1 mL) was then added to the vessel, followed by solvent removal in the same way. Two more additions and evaporations of dry acetonitrile were performed to ensure complete removal of  $H_2O$ . A lyophilized nanoparticle sample (5.7 mg) was dissolved in 3 mL dry acetonitrile and added to the vessel. The vessel was sealed and heated at 120 °C for 60 min. In order to displace the excess mesylates,  $K^{19}F$  (1.5 mg) and kryptofix 222 (6.5 mg) in 0.5 mL acetonitrile were added to the vessel. The vessel was sealed and heated for an additional 30 minutes at 80 °C. At this point the reaction mixture was diluted with water and passed through a column containing Dowex strongly acidic macroreticular ion exchange resin, followed by a short plug of alumina. RadioTLC was used to analyze the radiochemical purity of the product.

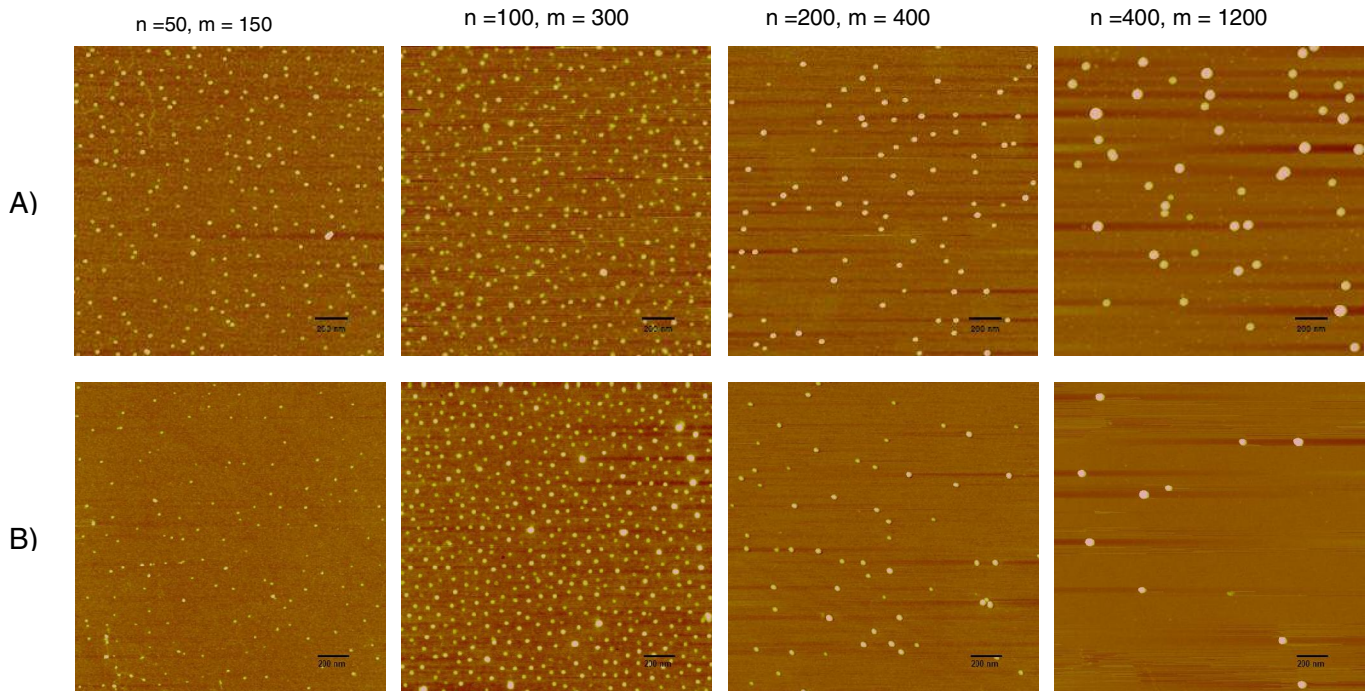


Figure S1. Comparison of micelles and nanoparticles by AFM. Column A: micelles, Column B: Crosslinked Nanoparticles. No structural or significant size changes are observed upon crosslinking.

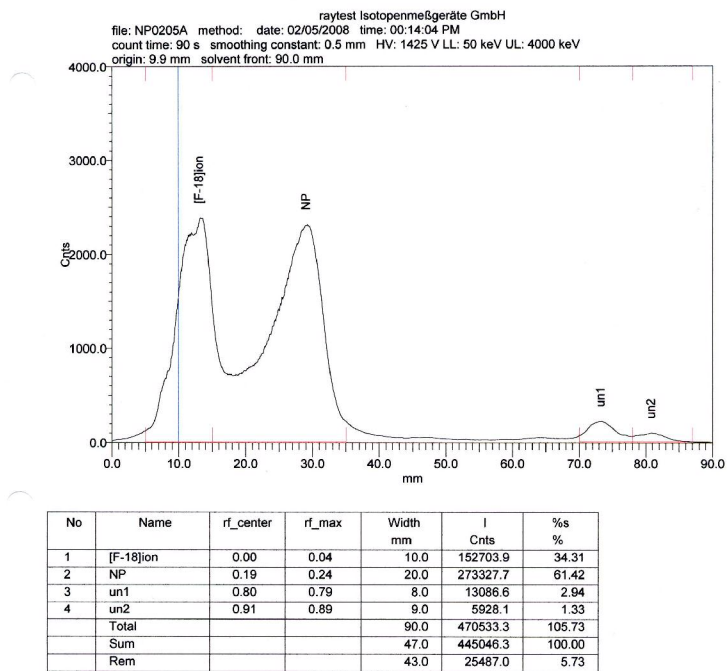


Figure S2: RadioTLC of radiofluorinated product.



## References

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