Supporting Information for:

Facile Preparation of Nanogels Using Activated Ester-Containing Polymers

*Jiaming Zhuang, Siriporn Jiwpanich, V. D. Deepak, and S. Thayumanavan**

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003

email: thai@chem.umass.edu

Materials and Methods:

Unless mentioned, all chemicals were used as received from Sigma-Aldrich. ^{1}H-NMR spectra were recorded on a 400 MHz Bruker NMR spectrometer while ^{19}F-NMR spectra were collected on a 300 MHz Bruker NMR spectrometer. Molecular weight of the polymers was measured by gel permeation chromatography (GPC, Waters) using a PMMA standard with a refractive index detector. THF was used as eluent with a flow rate of 1mL/min. Dynamic light scattering (DLS) measurements were performed using a Malvern Nanozetasizer. FTIR spectra were recorded on a Perkin Elmer spectrometer.

Synthesis of pentafluorophenyl acrylate PFPA: Monomer was synthesized by using a previously reported procedure. Briefly, pentafluorophenol (5.40g, 29.3 mmol) and 2,6-lutidine (3.80mL, 32.7mmol) were dissolved in dry dichloromethane (50.0 mL). The above solution was cooled in an ice bath and then acryloyl chloride was added (2.65mL, 32.7mmol). After stirring at ambient temperature for 12 hours, the reaction mixture was washed with water. The organic layer was collected, and dried

over anhydrous sodium sulfate. Crude product was further purified by flash chromatograph to afford pure product. Yield: 54%. ^{1}H NMR (400MHz, CDCl3) δ: 6.74 (d, 1H), 6.36 (q, 1H), 6.19 (d, 1H). ^{19}F NMR (300 MHz, CDCl3) δ: -152.5 (2F, d), -157.9 (1F, t), -162.3 (2F, d).

Synthesis of random copolymer PPFPA-r-PEGMA : To a Schlenk-flask, pentafluorophenyl acrylate (500.0 mg, 2.1mmol), poly(ethylene glycol) methyl ether methacrylate (428.0 mg, 0.9 mmol), recrystallized azodiisobutyonitrile (AIBN) (2.5 mg, 0.015 mmol), and 4-cyano-4-((thiobenzoyl)-sulfanyl) pentanoicacid (33.5 mg, 0.120 mmol) were mixed in 1, 4-dioxane (900 μL). The solution mixture was subjected to three freeze-pump-thaw cycles. The sealed flask was immersed in a preheated oil bath at 75 °C. The polymerization reaction was allowed to proceed for 5 days. The reaction was stopped by immersing the reaction flask in cold water. After the removal of 1, 4-dioxane, the mixture was precipitated in hexane. The resulting mixture was dissolved in THF and then precipitated in hexane. The same operation was repeated one more time to afford the pure polymer. Yield 90 %: ^{1}H NMR (400MHz, CDCl3) δ: 4.0-4.2 ppm, 3.5-3.8 ppm, 3.3-3.4 ppm, 2.7-3.2 ppm, 0.9-2.6 ppm. ^{19}F NMR (300 MHz, $CDCl_3$) δ: -152 to -155 ppm (2F), -158 to -160 ppm (1F), -164 to -166 ppm (2F). GPC (THF) Mn: 9.5 kDa. PDI: 1.3. By comparing the integral of the methylene protons adjacent to the ester in the polyethylene glycol unit and the polymer backbone proton in both the polyethylene glycol and the pentafluorophenyl units, the molar ratio was found to be 3:7 (PEGMA: PFPA).

Nanogel preparation in THF: 4.0 mg of polymer was dissolved in a known volume of dry THF to make a polymer solution with the desired concentration. To the polymer solution was added 0.50 equivalents of cross-linker with respected to the PFP groups and 1 equivalent of diisopropylethylamine (DIPEA). The solution was then heated at 50 °C for 4 hours to afford 100% cross-linked nanogel. The cross-linking reaction was characterized by FTIR. H_2O was added to the nanogel solution and the THF was evaporated by stirring the solution in air for 24 hours. The volume of nanogel solution was adjusted by adding water to afford the desired concentration. Preparation of the nanogel loaded with DiI(DiIC18(3)) follows the same procedure using a polymer solution mixed with 1wt% DiI. After cross-

linking and evaporation of THF, the nanogel solution was further purified by triplicate dialysis in milliQ water for 3 days.

Nanogel preparation in water: 4.0 mg of polymer solution was dissolved in H_2O to afford a polymer solution with the desired concentration. To the polymer solution, 0.50 equivalents of cross-linker with respect to the PFP groups and 1 equivalent of diisopropylethylamine (DIPEA) were added. The polymer solution was heated at 50 °C for 4 hours to afford 100% cross-linked nanogel.

Nanogel modification: 400 μL of 10.0 mg/mL polymer solution in THF was half cross-linked by the addition of 0.25 equivalents of CYS and 0.50 equivalents of DIPEA with respect to the PFP groups. After heating at 50 °C for 4 hours, 2.0 equivalents of isopropylamine (IPA) or N,N-dimethylethylenediamine (DMEDA) with 2 equivalents of DIPEA (with respect to the remaining PFP groups after cross-linking) were added to the nanogel solution and heated at 50 °C for another 4 hours. Cross-linking and post-nanogel substitution were monitored by FTIR. Water was added to the modified nanogel solution. THF was evaporated by stirring the sample in air for 24 hours. The nanogel solution was further purified by triplicate dialysis in milliQ water for 3 days.

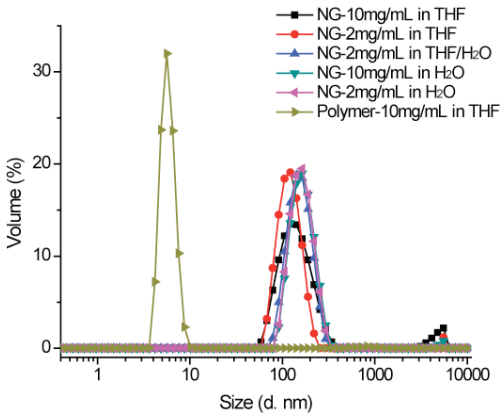

Figure S1. Size distribution of nanogel cross-linked by HMDA and dispersed in different solvents

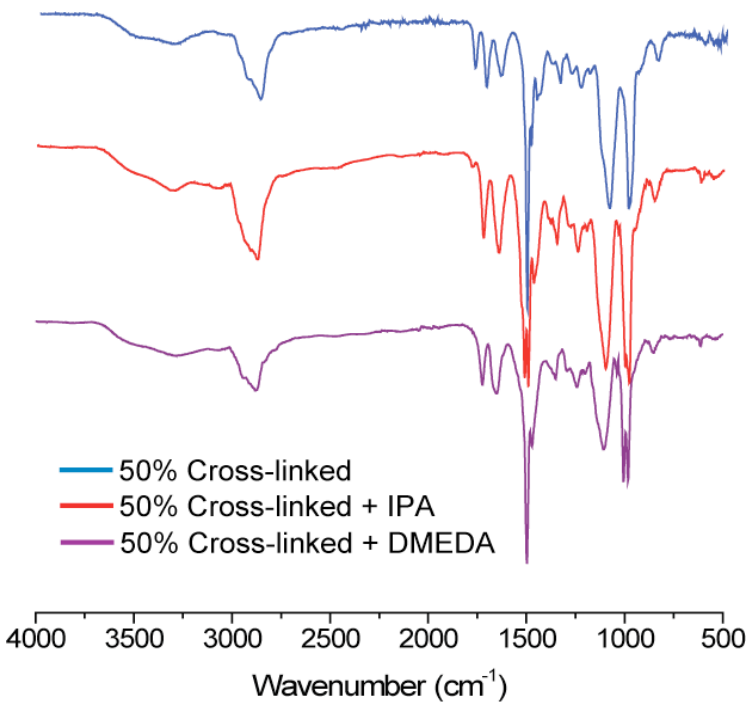

Figure S2. FTIR spectrum of nanogel and nanogel modified by isopropylamine (IPA) and N,N-dimethylethylenediamine (DMEDA)

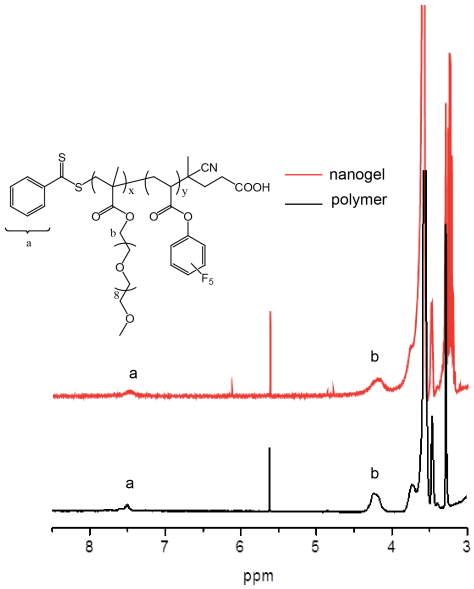

Figure S3. End group analysis for polymer and nanogel by ^{1}HNMR