Supporting Information:

Polymer Cross-linking: A Nanogel Approach to Enhancing the Relaxivity of MRI Contrast Agents

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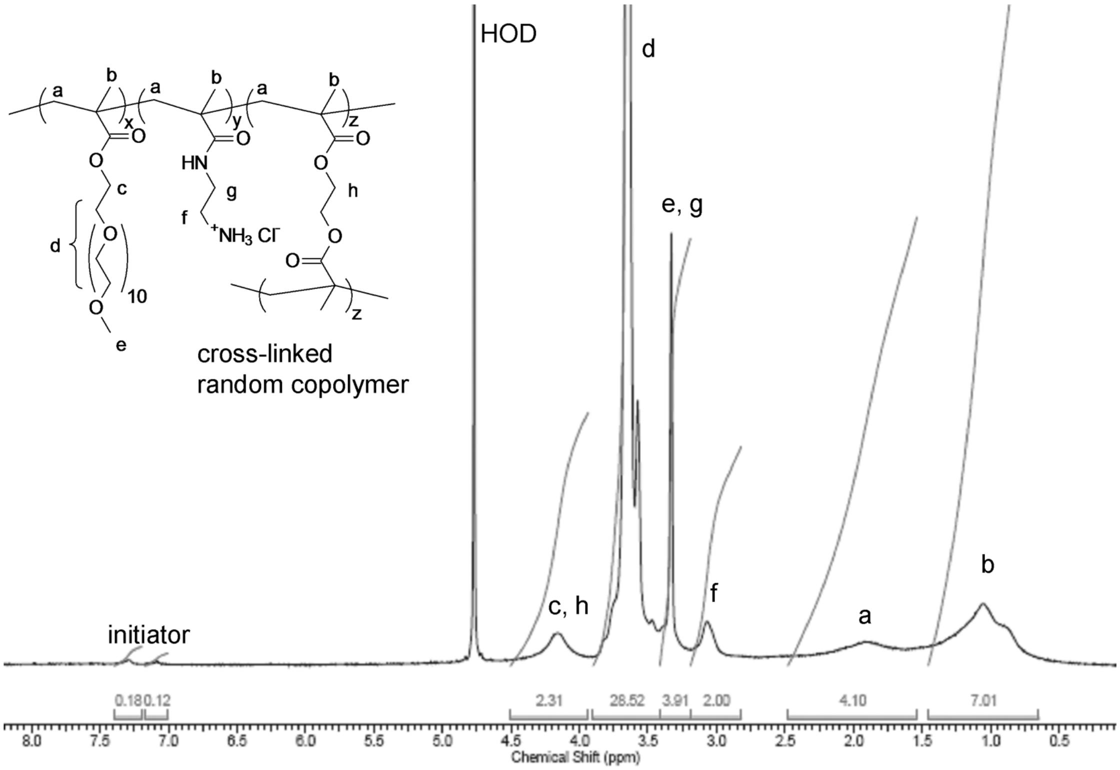

Figure S1. ^{1}H NMR spectrum of nanogel **4** (400 MHz, D_2O).

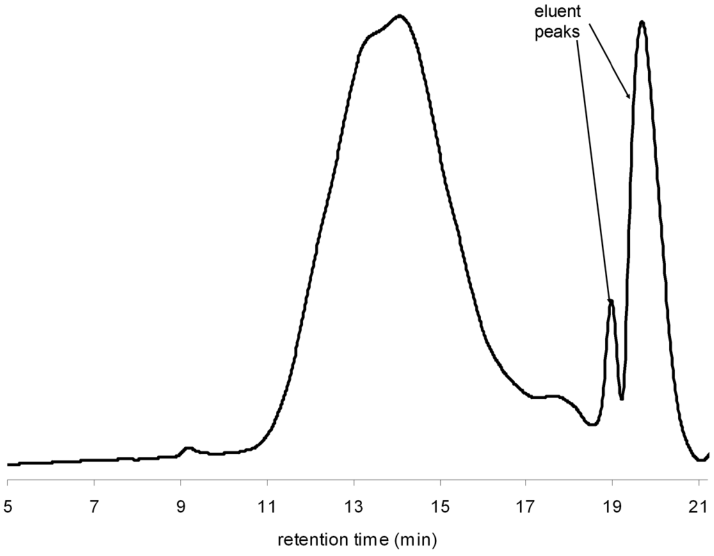

Figure S2. Size exclusion chromatogram of nanogel **4** (DMF with 10 mM LiBr and 1% (v/v) NEt_3, detection based on differential refractive index).

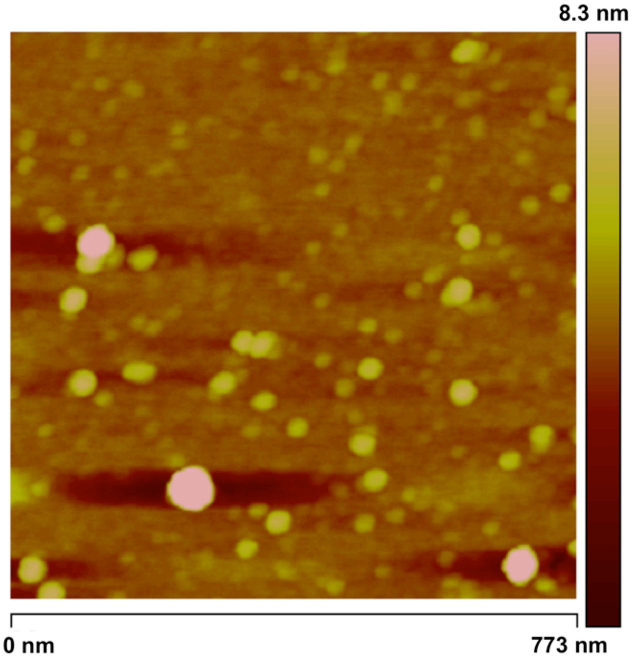

Figure S3. AFM image of nanogel **6**.

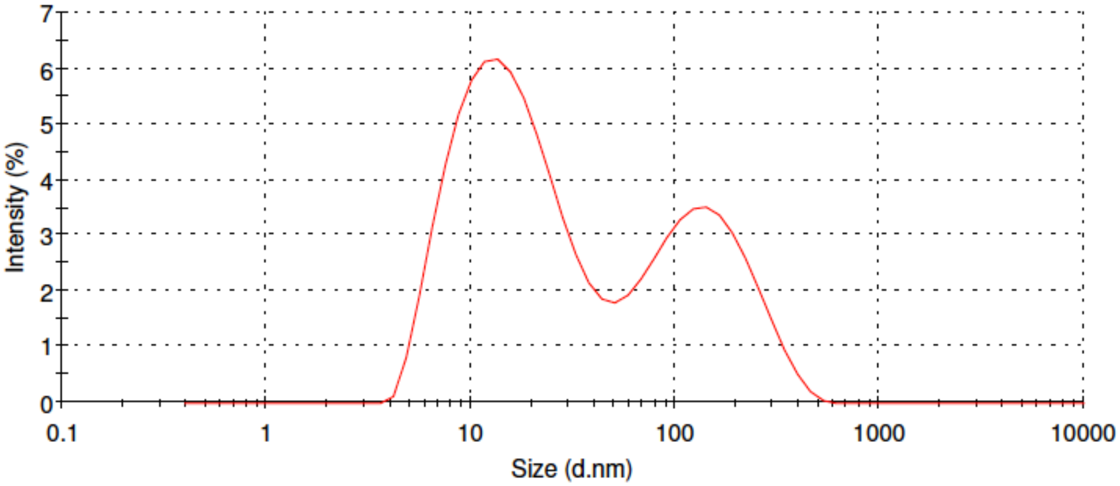

Figure S4. Size distribution by intensity of the nanogel **4**. Z-average size is 20 nm. As shown by the larger peak at ~150 nm, a small degree of aggregation is present but this is not present in the volume distribution (Figure 1 in manuscript) as large objects scatter much more strongly than small ones and thus account for a very small volume fraction of the sample.

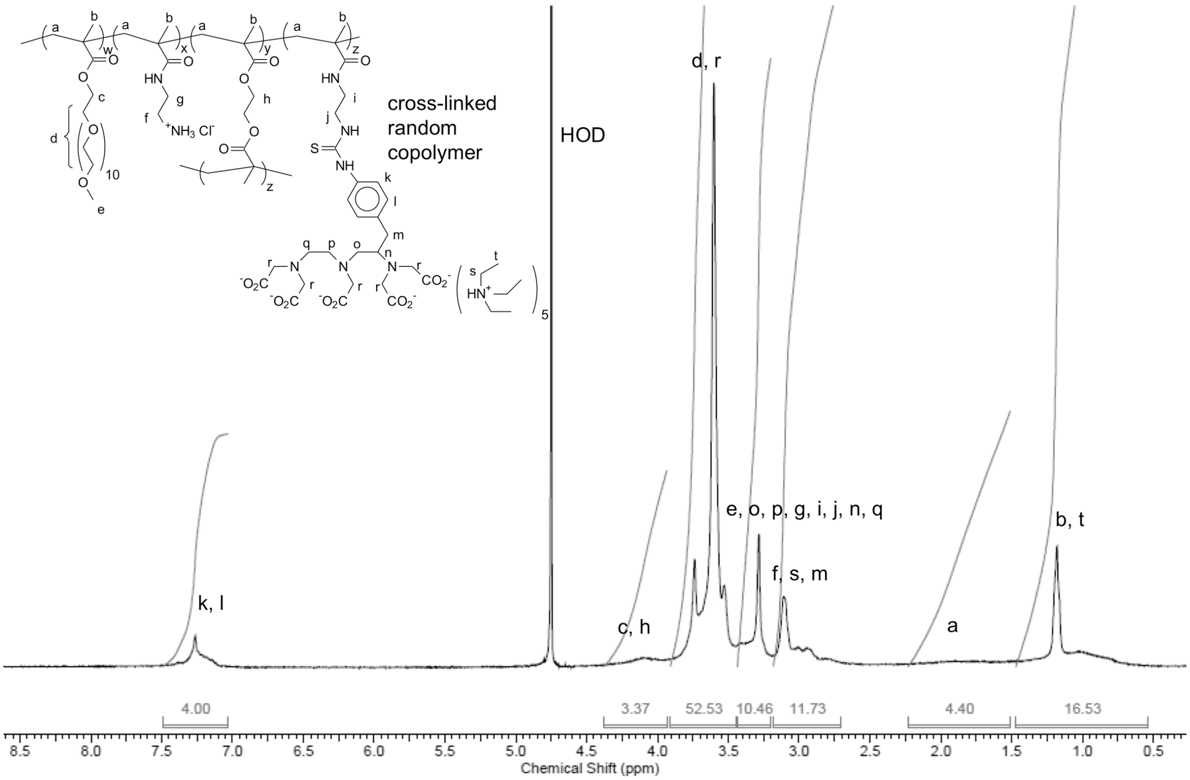

Figure S5. ^{1}H NMR spectrum of functionalized nanogel **5** (400 MHz, D_2O).

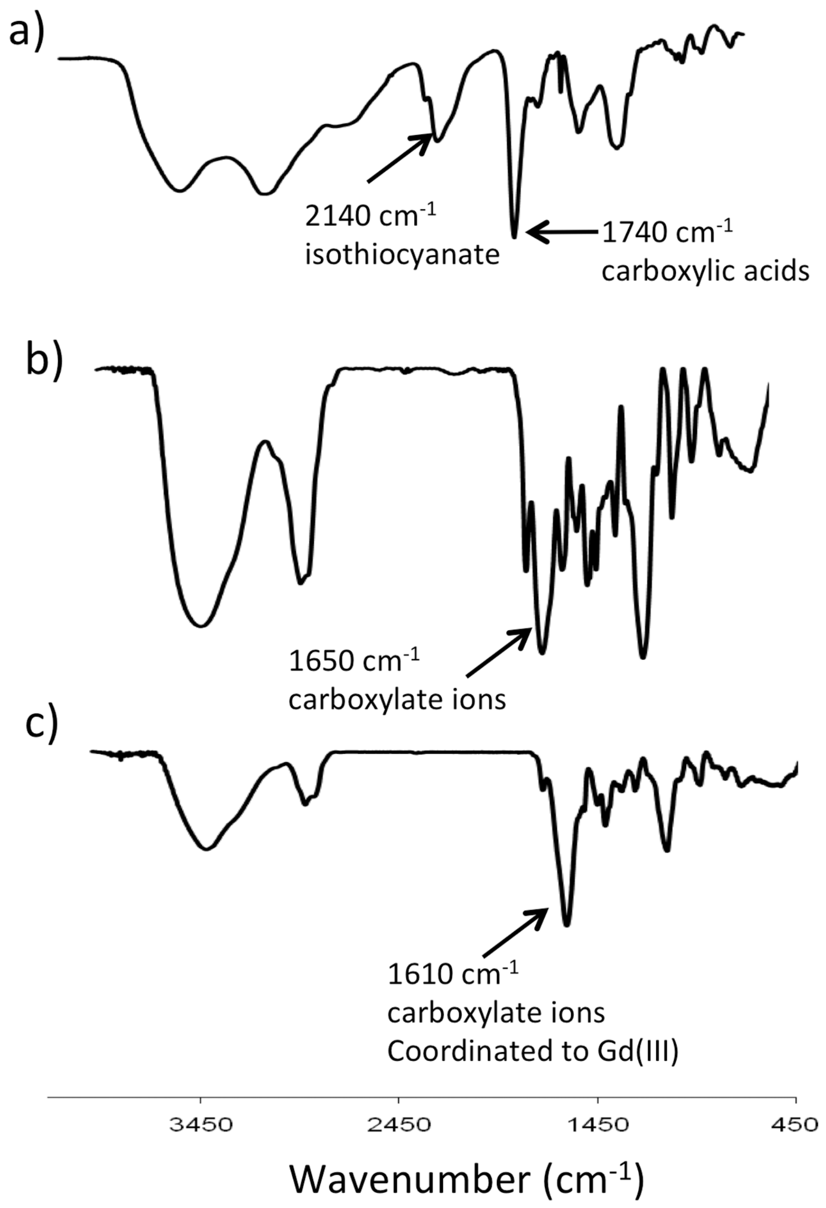

Figure S6. Infrared spectra of a) the isothiocyanate derivative of DTPA (*p*-SCN-Bn-DTPA), b) nanogel **5**, and c) nanogel **6** illustrating the successful conjugation of the chelate and coordination of Gd(III).

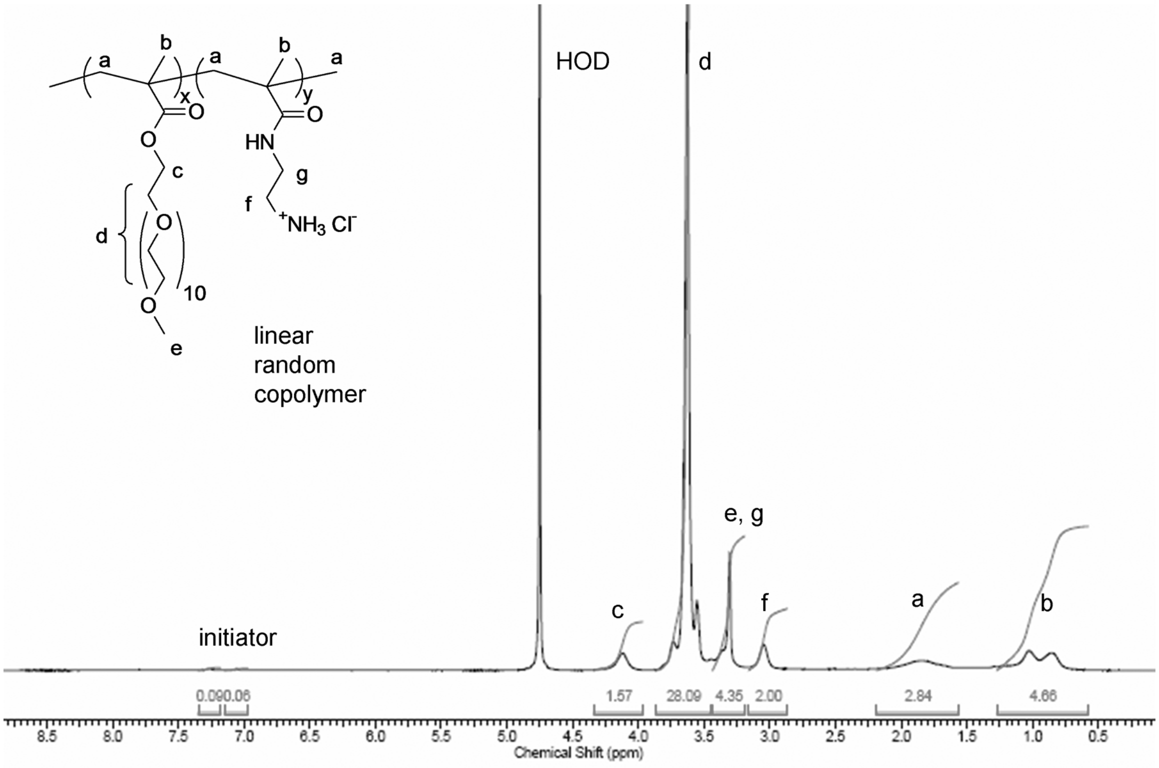

Figure S7. ^{1}H NMR spectrum of control linear polymer **7** (400 MHz, D$_2$O) illustrating shaper peaks than the corresponding NMR spectrum of nanogel **4**.

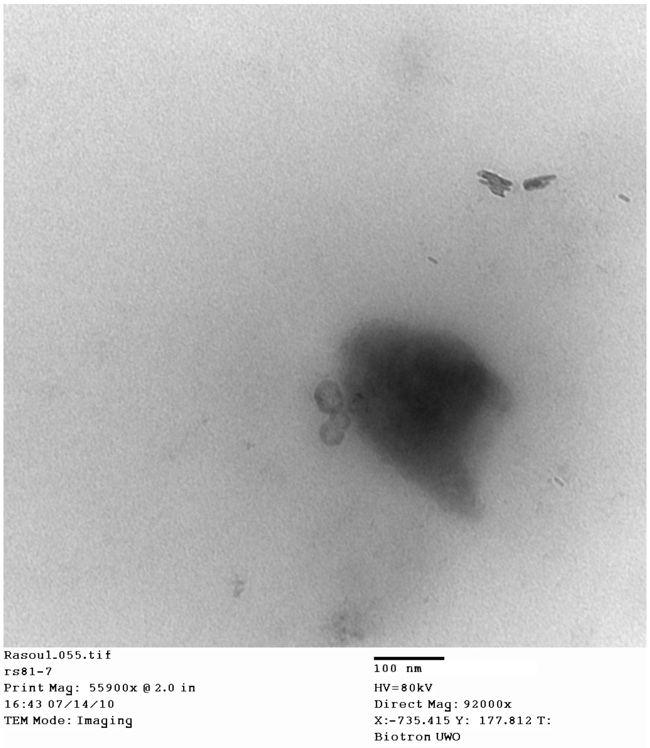

Figure S8. Transmission electron micrograph of linear polymer **7**, illustrating the formation of random aggregates rather than spherical particles.

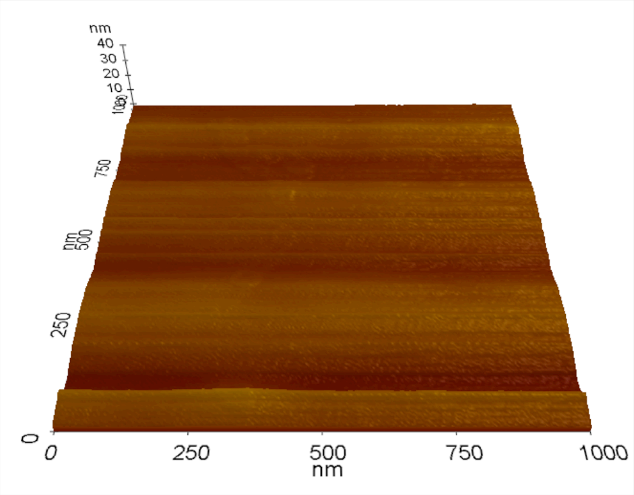

Figure S9. Atomic force microscopy image of linear polymer **7** showing the absence of spherical aggregates.

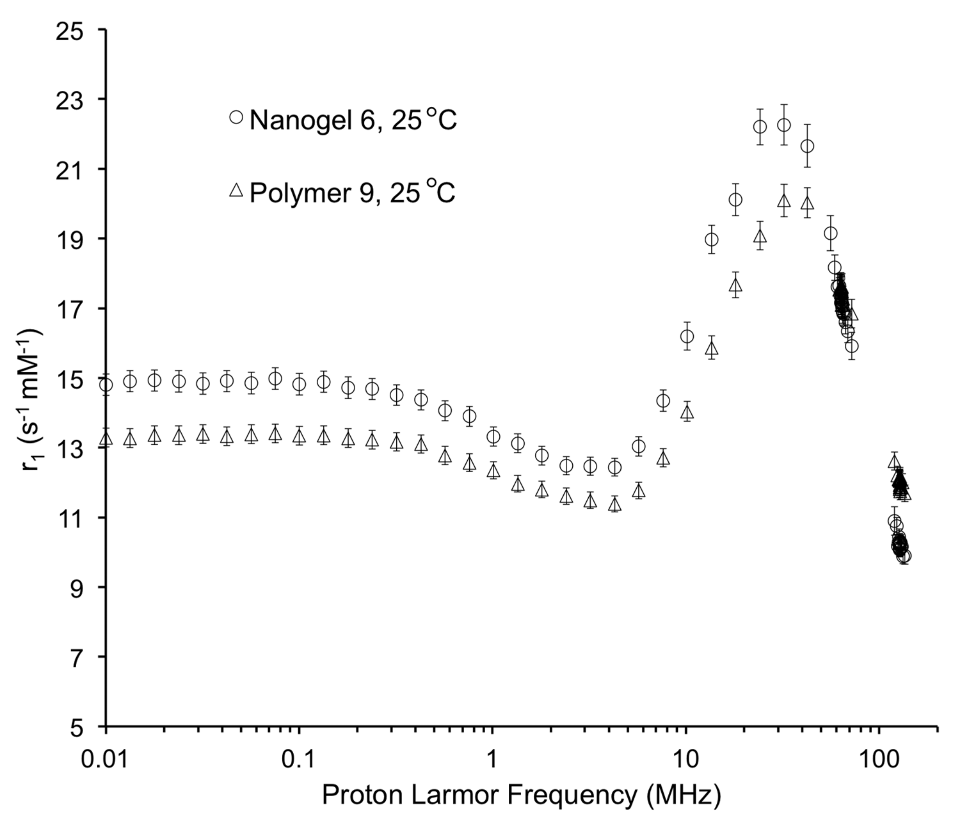

Figure S10. Longitudinal relaxivity (r_1) of nanogel **6** and control linear polymer **9** in phosphate buffer (0.1 M, pH 7.4) as a function of field strength at 25 °C.

NMRD Modeling

Longitudinal relaxation was modeled using a modification of the Solomon-Bloembergen-Morgan theory formulated by R. Lauffer.(1) Contributions from the inner hydration sphere were included as:

$$\left[\frac{1}{T_1}\right]_{IS} = \frac{[\mathrm{M}]}{[\mathrm{H_2O}]}\frac{q_{IS}}{T_{1M}+\tau_m}$$

where:

$\left[\frac{1}{T_1}\right]_{IS}$ is the spin-lattice relaxation rate due to inner-sphere interactions,

[M] is the molar concentration of the paramagnetic species,

[H_2O] is the molar concentration of water

q_{IS} is the inner-sphere hydration number

$T_{1\mathrm{M}}$ is the relaxation time for bound inner-sphere water molecules and

τ_{m} is the water residency time.

The inner sphere spin-lattice relaxation rate including dipolar and contact interactions was calculated from the following formula:

$$\frac{1}{T_{1M}} = \left(\frac{2}{15}\right)\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\gamma_H^2 g_e^2 S(S+1)\mu_B^2}{r_{GdH}^6}\left[\frac{3\tau_c}{1+\omega_H^2\tau_c^2}+\frac{7\tau_c}{1+\omega_S^2\tau_c^2}\right] + \frac{2}{3}S(S+1)\left(\frac{A}{\hbar}\right)^2\left[\frac{\tau_e}{1+\omega_S^2\tau_c^2}\right].$$

Constants in this equation include:

μ_0, the magnetic permeability of vacuum,

γ_H, the gyromagnetic ratio for protons,

g_e, the electronic g-factor,

S, the total electronic spin for the metal ion,

μ_B, the Bohr Magneton,

r_{GdH}, the metal ion-proton separation and

$\frac{A}{\hbar}$, the electron-nuclear hyperfine coupling constant.

ω_H and ω_S are respectively, the proton and electron Larmor precessional frequencies (rad/s) in the applied magnetic field.

The dipole-dipole correlation time, τ_c, depends on the longitudinal electronic spin relaxation time, T_{1e}, the water residency time, τ_m and the rotational correlation time, τ_R as:

$$\frac{1}{\tau_c} = \frac{1}{T_{1e}} + \frac{1}{\tau_m} + \frac{1}{\tau_R}\,.$$

The longitudinal electronic spin relaxation rate has the following dependency:

$$\frac{1}{T_{1e}} = B\left[\frac{1}{1+\omega_S^2\tau_v^2}\right] \text{ where } B = \frac{1}{5\tau_{S0}}\,.$$

Finally, the scalar relaxation time, τ_e, is equal to:

$$\frac{1}{\tau_e} = \frac{1}{T_{1e}} + \frac{1}{\tau_m}.$$

The quantities, S, r_{GdH}, q and $\frac{A}{\hbar}$ were held at fixed values of 7/2, 0.31 nm, 1 and 3×10^6 rad/s respectively.(2,3) Remaining parameters, τ_m (water residency time), τ_R (rotational correlation time), τ_v (correlation time for modulation of the transient zero-field splitting) and τ_{S0} (electronic relaxation time at zero field) where determined from a non-linear least-squares fit of this relaxation model to relaxivity data from NMRD measurements using even weighting of the data. The fitted parameters and their uncertainties (one standard deviation) are given in Table S1. A graph of the typical fitting results is illustrated in Figure S9.

Table S1. NMRD Fitting Results.

		Nanogel 6		**Polymer 9**	
Parameter	**Units**	**25°C**	**37°C**	**25°C**	**37°C**
τ_v	ps	39.4 ± 2.6	34.9 ± 1.9	40.2 ± 2.5	38.8 ± 2.5
τ_R	ns	2.72 ± 0.11	2.72 ± 0.10	1.68 ± 0.08	1.56 ± 0.08
τ_m	ns	576.4 ± 9.5	568.2 ± 8.5	536 ± 11	624 ± 12
τ_{S0}	ps	313 ± 12	261 ± 8.1	247.3 7.8	225.1 ± 7.8

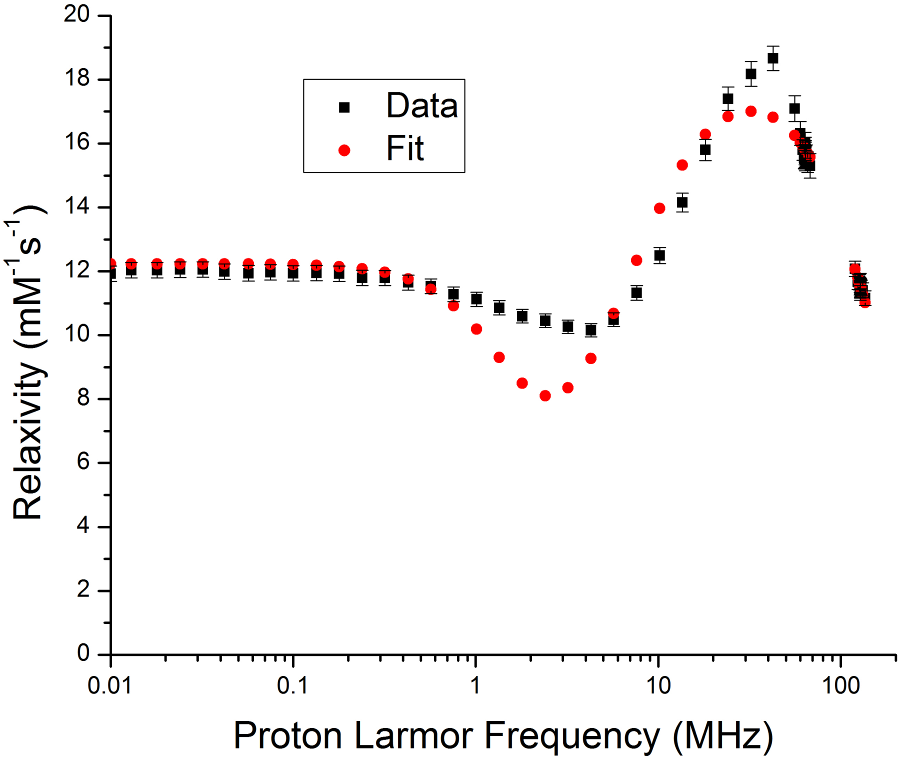

Figure S11: Relaxivity of Nanogel 6. The Lauffer model for inner-sphere dipole-dipole relaxation (red circles) has been fit to relaxivities (black squares) derived from NMRD data at 37°C. The error bars represent a measurement uncertainty of one standard deviation.

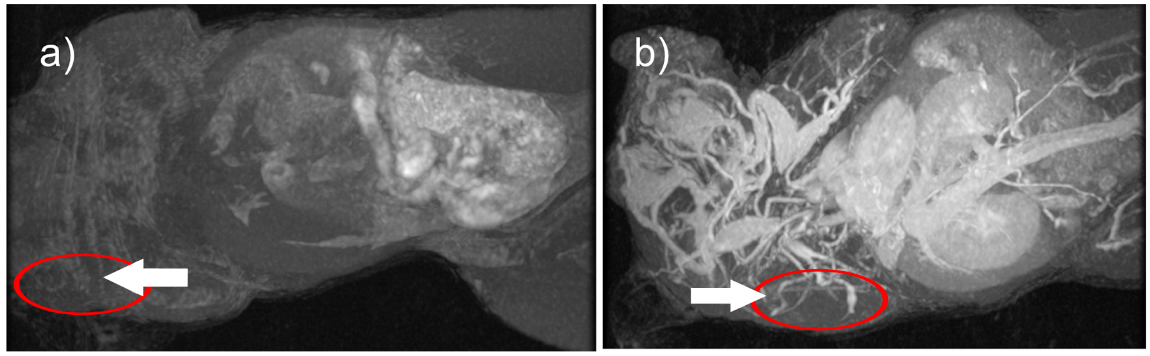

Figure S12. Additional MRI images of a tumor-baring animal injected with nanogel **6**. (a) Pre-contrast image, (b) post-contrast image. The location of the tumor is highlighted by the red ovals in both images. The arrows highlight the difference in the contrast in the vasculature between the pre- and post-contrast images.

References:

1. R. B. Lauffer, *Chem. Rev*. 1987, **87**, 901.
2. P. Caravan, A. V. Astashkin, A. M. Raitsimring, *Inorg. Chem.* 2003, **42**, 3972.
3. P. Caravan, N. J. Cloutier, M. T. Greenfield, S. A. McDermid, S. U. Dunham, J. W. M. Bulte, J. C. Amedio, R. J. Looby, R. M. Supkowski, W. D. Horrocks, T. J. McMurry, R. B. Lauffer. *J. Am. Chem. Soc.* 2002, **124**, 3152.