Supporting Information

Reversible Thermoresponsive Peptide/PNIPAM Hydrogels for Controlled Drug Delivery

Meiwen Cao,[*,†] Yu Wang,[†] Xuzhi Hu,[‡] Haoning Gong,[‡] Ruiheng Li,[‡] Henry Cox,[‡] Jing Zhang,[‡] Thomas A. Waigh,[‡,+] Hai Xu, [*,†] and Jian Ren Lu[*,‡]

[†] State Key Laboratory of Heavy Oil Processing and Centre for Bioengineering and Biotechnology, College of Chemical Engineering, China University of Petroleum (East China), 66 Changjiang West Road, Qingdao 266580, China

[‡] Biological Physics Laboratory, School of Physics and Astronomy, University of Manchester, Schuster Building, Oxford Road, Manchester M13 9PL, U.K.

+ Photon Science Institute, University of Manchester, Oxford Rd., Manchester, M13 9PL, U.K.

Corresponding Authors

* E-mail: mwcao@upc.edu.cn (M.C.); xuh@upc.edu.cn (H.X.); j.lu@manchester.ac.uk (J.R.L.)

Total of 5 figures, 2 tables and 6 pages in the SI document

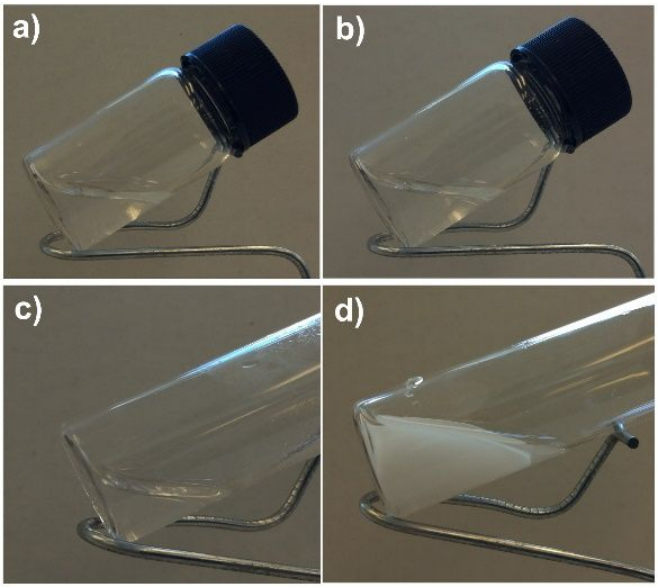

Figure S1. The photographs showing the state of the free solutions of I_3K (8 mM) and PNIPAM (20 mg/mL) at different temperatures: (a) I_3K at 25 °C, (b) I_3K at 40 °C, (c) PNIPAM at 25 °C, and (d) PNIPAM at 40 °C.

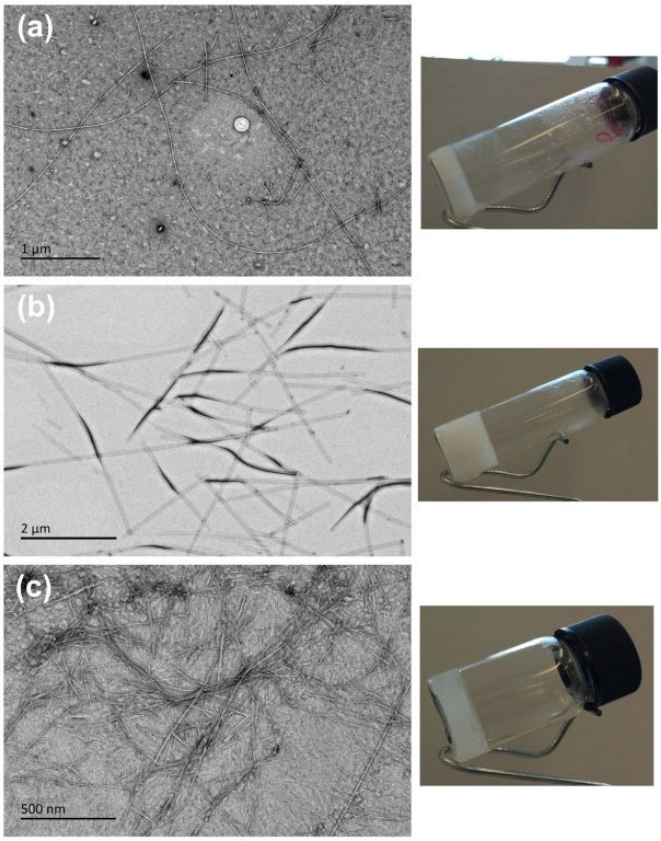

Figure S2. TEM images of the self-assembled structures (a) A_6K (4mM), (b) I_3QGK (4 mM), and (c) Fmoc-FF-OH (3 mM). A_6K self-assembles into long nanofibers with

micrometer length and diameter of 8.0 ± 1.5 nm. I_3QGK forms nanoribbons with micrometer length and width of 30–55 nm. Fmoc-FF-COOH produces micrometer long fibrils with diameters of 5.5 ± 0.5 nm and 10.0 ± 1.0 nm and some fibril bundles. The right panel shows the corresponding photographs of the peptide/PNIPAM mixtures at 40 °C, (a) A_6K (4 mM) + PNIPAM (15 mg/mL), (b) I_3QGK (4 mM) + PNIPAM (10 mg/mL), and (c) Fmoc-FF-OH (3 mM) + PNIPAM (5 mg/mL).

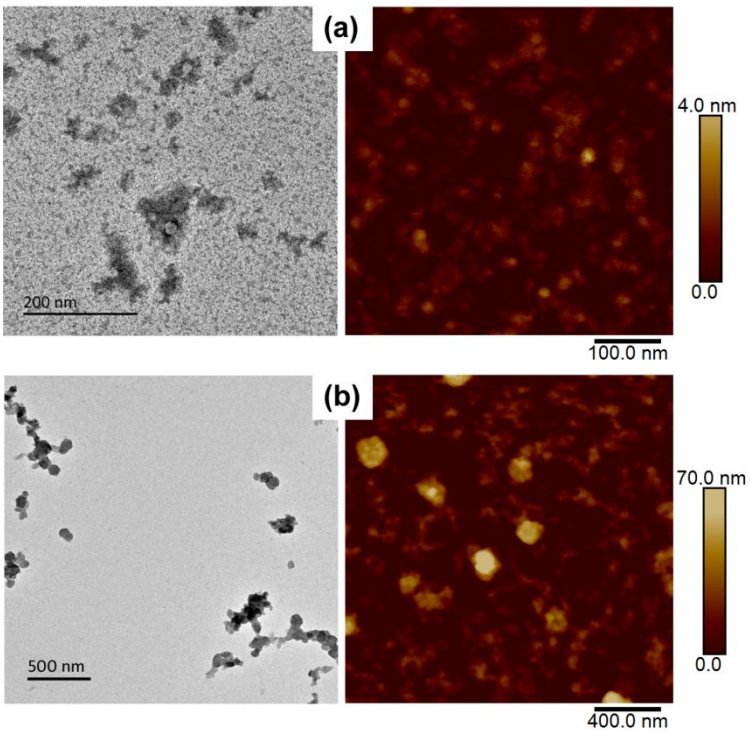

Figure S3. TEM (left panel) and AFM (right panel) images of PNIPAM aggregates (10 mg/mL, Tris buffer pH 7.4) at different temperatures, (a) 25 °C and (b) 40 °C. PNIPAM at 25 °C produced loose thin aggregates due to surface-induced concentrating effect and aggregation. PNIPAM at 40 °C produced larger dense aggregates due to temperature-induced coil-to-globule transition, though the surface effects could be completely excluded.

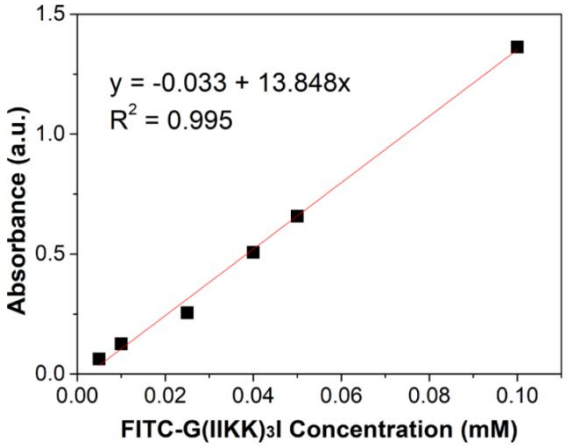

Figure S4. The standard calculation curve derived by linear fitting of the absorbance at 495 nm of FITC-G(IIKK)$_3$I-NH$_2$ solutions of different concentration.

Table S1. The best-fitted structural parameters for the SANS data as shown in Figure 3. The unit for the sld (scattering length density) is Å^{-2}.

		I_3K		**PNIPAM**		**PNIPAM/I_3K**	
temperature		25 °C	40 °C	25 °C	40 °C	25 °C	40 °C
fitting models		Flexible Cylinder Model (FCM)		Debye	Ellipsoid Model (EM)	Debye + FCM	FCM + EM
Fitting parameters	Kuhn_length	87Å	92Å	—	—	—	—
	Length	1000Å	1000Å	—	—	—	—
	Radius	48.9Å	48.7Å	—	—	—	—
	Radius_a	—	—	—	2544Å	—	2754Å
	Radius_b	—	—	—	3541Å	—	5597Å
	p1_r_g	—	—	83.5Å	—	76.5Å	—
	p1_scale	—	—	0.45	0.08	0.70	0.65
	p1_sldCyl	3.22×10^6	3.17×10^6	—	5.11×10^6	—	5.46×10^6
	p1_sldSolv	5.69×10^6	5.98×10^6	—	6.08×10^6	—	6.01×10^6
	p2_Kuhn_length	—	—	—	—	72Å	95
	p2_length	—	—	—	—	909Å	>1000Å
	p2_radius	—	—	—	—	53Å	49.3Å
	p2_scale	—	—	—	—	1.3	1.54

p2_sldCyl	—	—	—	—	4.49×10^{6}	5.42×10^{6}
p2_sldSolv	—	—			6.26×10^{6}	5.54×10^{6}
scale_factor	—	—	—	—	0.23	0.36

The models used for fitting the small angle neutron scattering (SANS) data are detailed as follows.

(1) The Debye Model:

The Debye model is for the linear polymer chain. The radius of gyration (r_g), a scale factor, and a constant background term are included in the calculation. The fundamental theory of the Debye Model can be found from reference [Roe et al., 2000][1].

(2) The Flexible Cylinder Model:

The fundamental theory of the flexible cylinder model can be found from references [Pedersen et.al, *Macromolecules* **1996**, *29*, 7602][2] and [Chen et. al, *Langmuir* **2006**, *22*, 6539][3].

In this model, the chain of contour length can be described as a chain of some number of locally stiff segments of length L_p (L_p: the persistence length, the length along the chain over which the flexible cylinder can be considered as a rigid rod). The Kuhn length = 2 × L_p. In the fitting parameters, the sldCyl and sldSolv represent SLD (chain/cylinder) and SLD (solvent), respectively.

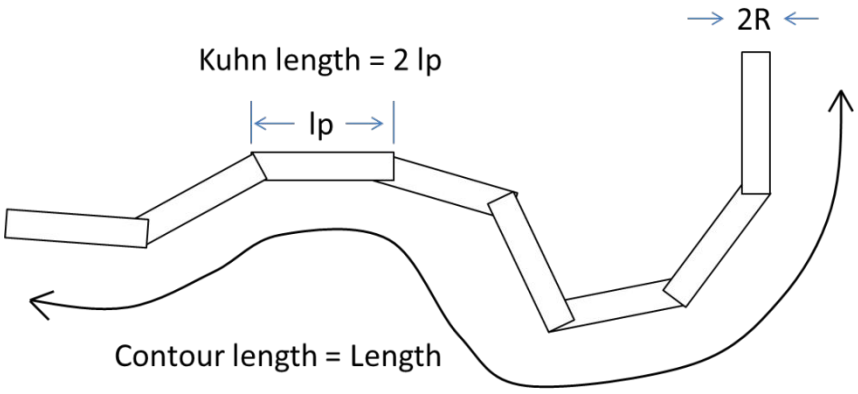

Figure S5. Scheme for the Flexible Cylinder Model.

(3) The Ellipsoid Model:

This model provides the form factor for an ellipsoid (ellipsoid of revolution) with uniform scattering length density. The form factor is normalized by the particle volume. The fundamental theory of the FlexCylEllipX Model can be found from reference [Feigin, 1987][4].

Table S2. The best-fitted structural parameters for the SANS data as shown in Figure 5c.

		I_3K	**$I_3K/G(IIKK)_3I$**
temperature		25 °C	25 °C
fitting models		FCM	FCM
Fitting parameters	Kuhn_length	11Å	9Å
	Length	4247Å	6042Å
	Radius	46.1Å	49.2Å
	sldCyl	3.58×10^{6}	3.69×10^{6}
	sldSolv	6.39×10^{6}	6.50×10^{6}

References:

1. Roe, R.-J., *Methods of X-Ray and Neutron Scattering in Polymer Science*, Oxford University Press, New York, **2000**.
2. Pedersen, J. S.; Schurtenberger, P., Scattering Functions of Semiflexible Polymers with and without Excluded Volume Effects. *Macromolecules* **1996,** *29* (23), 7602-7612.
3. Chen, W.-R.; Butler, P. D.; Magid, L. J., Incorporating Intermicellar Interactions in the Fitting of SANS Data from Cationic Wormlike Micelles. *Langmuir* **2006,** *22* (15), 6539-6548.
4. Feigin, L.; Svergun, D. I., *Structure Analysis by Small-Angle X-Ray and Neutron Scattering*. Springer: Plenum, New York, **1987**.