

## **Supplementary Information**

for: **Dendritic Polyglycerol Anions for the Selective Targeting of Native and Inflamed Articular Cartilage**

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## Synthesis

### Dendritic polyglycerol scaffold

Dendritic polyglycerol (dPG) **1** as the starting polymer was synthesized in one step according to the literature via anionic ring opening polymerization of glycidol by using deprotonated pentaerythritol as the starter.<sup>1</sup> The polymer shows a number average molecular weight of  $M_n = 6,000 \text{ g mol}^{-1}$ , a degree of branching (DB) of  $\approx 60\%$ , and a polydispersity index (PDI) of  $\approx 1.6$ , bearing on average  $\approx 81$  hydroxyl groups per molecule. Molecular weights of further derivatives were calculated from the particular conversion as determined by  $^1\text{H-NMR}$  spectroscopy or from the sulfur content obtained by elemental analysis.

### Alkyne precursors for click reaction

The bisphosphonate- and phosphate-functionalized alkyne precursors were prepared as previously described.<sup>2,3</sup>

### Unlabeled dendritic polyglycerol anions

The non-dye-labeled dPG anions **S5**, **S15**, and **S16** were synthesized according to previously published procedures by sulfation of dPG or click-reaction of dPG azide using the respective alkyne precursor.<sup>2-4</sup> The specification of the polyanions can be found in **Table S2**.

### General procedure for mesylation of dendritic polyglycerol

dPG mesylate was prepared as previously described by reacting dendritic polyglycerol with mesyl chloride.<sup>3,5</sup> To a solution of dPG ( $M_n = 6,000 \text{ g mol}^{-1}$ , 81 OH groups per molecule) in anhydrous pyridine mesyl chloride was added dropwise over 30 min at  $0^\circ\text{C}$ . The resulting mixture was stirred for 24 h at room temperature. Water was added, the solvent was removed, and the residue was dialyzed in either methanol (dF = 17%) or acetone (dF = 50%, dF = 100%). Evaporation of the solvent gave the respective title compound.

### General procedure for azidation of dendritic polyglycerol mesylate

dPG azide was prepared as previously published by reacting dPG mesylate with sodium azide.<sup>3,5</sup> Briefly, dPG mesylate was solved in anhydrous DMF and 3 eq. sodium azide per mesyl group were added. The mixture was stirred for 3 d at  $70^\circ\text{C}$ , cooled to room temperature and filtered. The solvent was removed and the resulting residue was redissolved in either methanol (dF = 17%) or chloroform (dF = 50%, dF = 100%). After filtration over celite the residue was dialyzed in either methanol (dF = 17%) or chloroform (dF = 50%, dF = 100%). Evaporation of the solvent gave the respective title compound.

### General procedure for reduction of dPG azide derivatives to dPG amine

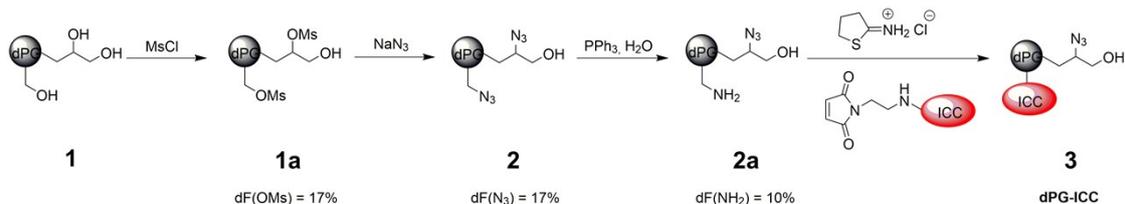
dPG amine derivatives were synthesized as previously described with  $\text{PPh}_3$  as the reducing agent.<sup>5</sup> The respective dendritic polyglycerol azide derivative was dissolved in water and 8 eq.  $\text{PPh}_3$  per polymer in THF were added. The mixture was stirred over night at room temperature. The solvent was removed and the residue was dialyzed in water. Freeze-drying gave the respective dPG amine.

### General procedure for dye coupling to dPG amine derivatives

Dye conjugation was conducted according to a previously described procedure with the respective dPG amine derivative and the dye maleimide.<sup>6</sup> The respective dendritic polyglycerol amine was dissolved in PBS, the pH of the solution was adjusted to pH 9 with DIPEA, and 2 eq. of 2-iminothiolane hydrochloride per polymer were added. The mixture was stirred for 15 min at room temperature, 2 eq. of dye maleimide in PBS were added, and the solution was stirred for 5 days at room temperature. The solvent was removed and the crude product was subjected to ultrafiltration in water. After concentration in vacuo, purification by SEC with Sephadex<sup>TM</sup> G-25 superfine, and subsequent freeze-drying, the respective dye labeled dPG anion was obtained.

### General procedure for click coupling of anionic alkynes to dendritic polyglycerol azide derivatives

Click coupling of the anionic alkyne to dPG azide was performed according to a previously published procedure.<sup>2,3</sup> Copper sulfate pentahydrate (10 mol% of alkyne) was dissolved in water and sodium ascorbate (25 mol% of alkyne) was added. The resulting yellow solution was adjusted to pH 9 with aqueous NaOH solution and the respective alkyne was added. The mixture was combined with the corresponding dendritic polyglycerol azide in water (dF = 17% ( $\text{N}_3$ ), dF = 50% ( $\text{N}_3$ ), 50% (S)) or THF (dF = 100% ( $\text{N}_3$ )) and stirred for 3 d at room temperature. The solvent was removed and the crude product was subjected to ultrafiltration using saturated aqueous EDTA/ sodium chloride solution for the first three cycles, followed by water for five cycles. Freeze-drying gave the respective title compound.



**Fig. S1** Reaction pathway for the synthesis of ICC-labeled dPG (**3**) via mesylation (**1a**), azidation (**2**), azide reduction (**2a**), and dye coupling (**3**) using 2-iminothiolane hydrochloride and ICC-maleimide.

#### Dendritic polyglycerol mesylate (dPGOMs, dF = 17%) (**1a**)

The title compound was prepared according to the general procedure for mesylation using 0.17 eq. mesyl chloride per OH group and was obtained as a yellowish oil.  $M_n = 7,100 \text{ g mol}^{-1}$ , dF = 17%, yield: 84%. <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ ): 5.60 – 3.20 (m, 10H, dPG backbone), 3.16 (s, 1H, CH<sub>3</sub>, OMs) ppm.

#### Dendritic polyglycerol azide (dPGN<sub>3</sub>, dF = 17%) (**2**)

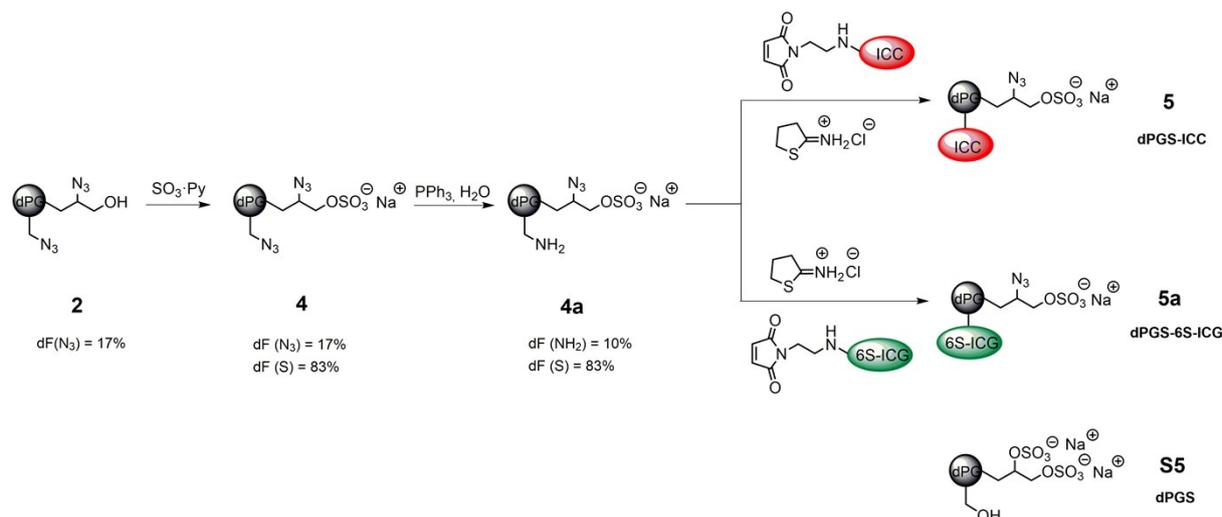
The title compound was prepared according to the general procedure for azidation from dendritic polyglycerol mesylate (**1a**) ( $M_n = 7,100 \text{ g mol}^{-1}$ , dF = 17% (OMs)) and was obtained as a yellowish oil.  $M_n = 6,350 \text{ g mol}^{-1}$ , dF = 17%, yield: 86%. <sup>1</sup>H-NMR (400 MHz, MeOD-*d*<sub>4</sub>,  $\delta$ ): 3.98 – 3.27 (m, dPG backbone) ppm.

#### Dendritic polyglycerol amine (dPGNH<sub>2</sub>, dF = 10%) (**2a**)

The title compound was synthesized from dendritic polyglycerol azide (**2**) ( $M_n = 6,350 \text{ g mol}^{-1}$ , dF = 17% (N<sub>3</sub>)) according to the general procedure for reduction of azides and was obtained as a yellowish oil.  $M_n = 6,150 \text{ g mol}^{-1}$ , dF = 10%, yield: 80%. <sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O,  $\delta$ ): 4.23 – 3.24 (m, dPG backbone) ppm. <sup>13</sup>C-NMR (176 MHz, D<sub>2</sub>O,  $\delta$ ): 79.6, 79.4, 78.2, 77.9, 73.0, 72.1, 70.9, 70.7, 70.4, 69.2, 68.9 (dPG-backbone), 62.6, 60.8 (*C*<sub>sec</sub>.N<sub>3</sub>, *C*<sub>prim</sub>.N<sub>3</sub>), 53.1, 42.7 (*C*<sub>sec</sub>.NH<sub>2</sub>, *C*<sub>prim</sub>.NH<sub>2</sub>) ppm. IR (dry film):  $\nu_{\text{max}} = 3358$  (s), 2871 (s), 2101 (w), 2035 (w), 1644 (w), 1591 (w), 1457 (m), 1406 (w), 1323 (m), 1261 (m), 1063 (s), 932 (m), 863 (m) cm<sup>-1</sup>.

#### ICC-labeled dendritic polyglycerol (dPG-ICC) (**3**)

The title compound was prepared according to the general procedure for dye coupling using ICC-maleimide and dendritic polyglycerol amine (**2a**). Freeze-drying gave the product as a pink solid.  $M_n = 6,150 \text{ g mol}^{-1}$ , dye loading = 0.09, yield: 91%. UV-Vis (PBS):  $\lambda_{\text{max}} = 554 \text{ nm}$ .



**Fig. S2** Reaction pathway for the synthesis of ICC- (**5**) and 6S-ICG-labeled dPGS (**5a**) via sulfation (**4**), azide reduction (**4a**), and dye coupling using 2-iminothiolane hydrochloride and ICC- (**5**) or 6S-ICG-maleimide (**5a**). Unlabeled dPGS (**S5**) was prepared by sulfation of dendritic polyglycerol (**1**).

### Highly sulfated dendritic polyglycerol azide (dPGS/N<sub>3</sub>, dF = 17% (N<sub>3</sub>), 83% (S)) (4)

The title compound was prepared according to a previously described procedure by reacting dendritic polyglycerol azide (**2**) ( $M_n = 6,350 \text{ g mol}^{-1}$ , dF = 17% (N<sub>3</sub>)) with SO<sub>3</sub> pyridine complex in anhydrous DMF.<sup>3,4</sup> Freeze-drying yielded the product as a colorless solid.  $M_n = 13,300 \text{ g mol}^{-1}$ , dF (S) = 83%, yield: 94%. <sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O,  $\delta$ ): 4.72 – 4.53 (m, 1H, C<sub>sec</sub>-HOSO<sub>3</sub>), 4.53 – 4.14 (m, 2H, C<sub>prim</sub>-H<sub>2</sub>OSO<sub>3</sub>), 4.14 – 3.30 (m, 4H, dPG backbone) ppm.

### Amine functionalized dendritic polyglycerol sulfate (dPGS/NH<sub>2</sub>, dF = 10% (NH<sub>2</sub>), 83% (S)) (4a)

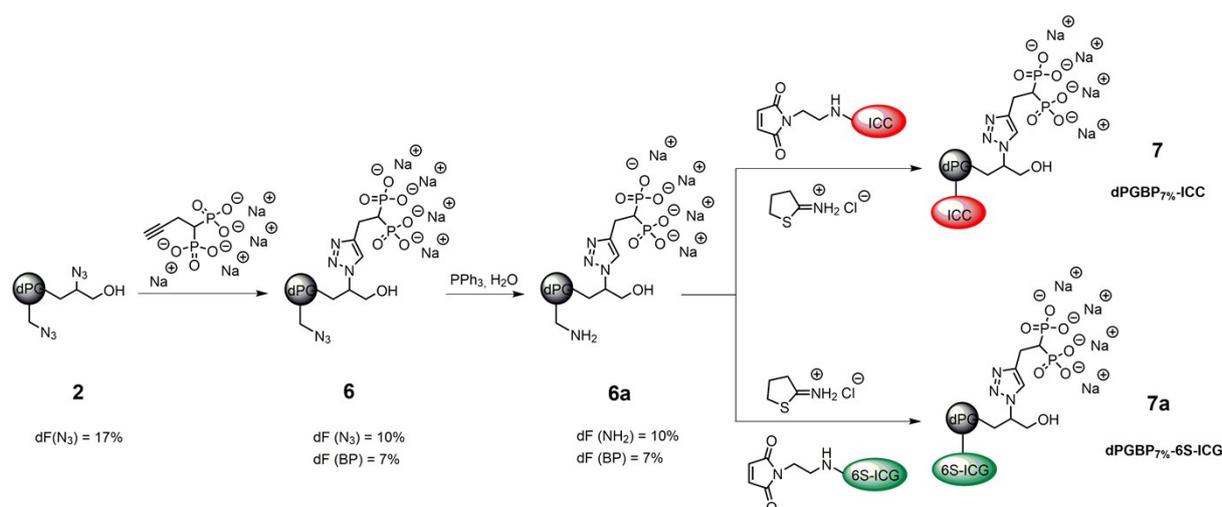
The title compound was prepared from azide-functionalized dPGS (**4**) ( $M_n = 13,300 \text{ g mol}^{-1}$ , dF = 17% (N<sub>3</sub>), 83% (S)) according to the general procedure for reduction of azides and was obtained as a colorless solid.  $M_n = 14,000 \text{ g mol}^{-1}$ , dF (NH<sub>2</sub>) = 10%, yield: 87%. <sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O,  $\delta$ ): 4.72 – 4.42 (m, 1H, C<sub>sec</sub>-HOSO<sub>3</sub>), 4.42 – 4.08 (m, 2H, C<sub>prim</sub>-H<sub>2</sub>OSO<sub>3</sub>), 4.08 – 3.30 (m, 4H, dPG backbone) ppm. <sup>13</sup>C-NMR (176 MHz, D<sub>2</sub>O,  $\delta$ ): 79.7, 79.4, 78.2, 78.0, 77.1, 75.6 (C<sub>sec</sub>-HOSO<sub>3</sub>, C<sub>prim</sub>-H<sub>2</sub>OSO<sub>3</sub>), 72.2, 71.6, 70.9, 70.7, 70.5, 69.8, 69.2, 68.9, 68.5, 68.2, 67.4, 66.7, 66.3 (dPG-backbone) 62.7, 60.9, 60.6 (C<sub>sec</sub>-N<sub>3</sub>, C<sub>prim</sub>-N<sub>3</sub>), 53.1 (C<sub>sec</sub>-NH<sub>2</sub>, C<sub>prim</sub>-NH<sub>2</sub>) ppm. IR (dry film):  $\nu_{\text{max}} = 3391 \text{ (s)}, 2881 \text{ (s)}, 2299 \text{ (w)}, 2103 \text{ (w)}, 1640 \text{ (w)}, 1459 \text{ (m)}, 1343 \text{ (w)}, 1220 \text{ (s)}, 1066 \text{ (s)}, 1005 \text{ (s)}, 937 \text{ (m)}, 873 \text{ (w)}, 782 \text{ (s)} \text{ cm}^{-1}$ .

### ICC-labeled dendritic polyglycerol sulfate (dPGS-ICC) (5)

The title compound was prepared according to the general procedure for dye coupling using ICC-maleimide and amine-functionalized dendritic polyglycerol sulfate (**4a**). Freeze-drying gave the product as a pink solid.  $M_n = 14,000 \text{ g mol}^{-1}$ , dye loading = 0.17, yield: 71%. UV-Vis (PBS):  $\lambda_{\text{max}} = 550 \text{ nm}$ .

### 6S-ICG-labeled dendritic polyglycerol sulfate (dPGS-6S-ICG) (5a)

The title compound was prepared according to the general procedure for dye coupling using 6S-ICG-maleimide and amine-functionalized dendritic polyglycerol sulfate (**4a**). Freeze-drying gave the product as a green solid.  $M_n = 14,000 \text{ g mol}^{-1}$ , dye loading = 1.1, yield: 84%. UV-Vis (PBS):  $\lambda_{\text{max}} = 785 \text{ nm}$ .



**Fig. S3** Reaction pathway for the synthesis of ICC- (**7**) and 6S-ICG-labeled dPGBP<sub>7%</sub> (**7a**) via partial click coupling (**6**), azide reduction (**6a**), and dye coupling using 2-iminothiolane hydrochloride and ICC- (**7**) or 6S-ICG-maleimide (**7a**).

### Low bisphosphonate-functionalized dendritic polyglycerol azide (dPGBP<sub>7%</sub>/N<sub>3</sub>, dF = 10% (N<sub>3</sub>), 7% (BP)) (6)

The title compound was prepared according to the general procedure for click coupling using dendritic polyglycerol azide (**2**) ( $M_n = 6,350 \text{ g mol}^{-1}$ , dF = 17% (N<sub>3</sub>)) and 10 eq. of the bisphosphonate alkyne per polymer. The product was obtained as a slightly brown solid.  $M_n = 8,150 \text{ g mol}^{-1}$ , dF (BP) = 7%, yield: 71%. <sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O,  $\delta$ ): 8.87 – 7.86 (m, 0.07H, triazole, NCH=C), 5.63 – 4.88 (m, 0.07H, CH-triazole), 4.67 – 4.37 (m, 0.14H, CH<sub>2</sub>-triazole), 4.36 – 3.37 (m, 5H, dPG backbone), 3.37 – 2.99 (m, 0.14H, CH<sub>2</sub>CHP<sub>2</sub>), 2.80 – 2.35 (m, 0.07H, CH<sub>2</sub>CHP<sub>2</sub>) ppm. <sup>13</sup>C-NMR (176 MHz, D<sub>2</sub>O,  $\delta$ ): 145.1 (triazole, NCH=C), 128.2, 126.1 (triazole, NCH=C), 79.8, 79.6, 78.3, 78.0, 72.3, 71.0, 70.8, 70.5, 69.3, 69.0, 68.5 (dPG backbone), 62.8, 62.0 (C<sub>sec</sub>-N<sub>3</sub>, C<sub>prim</sub>-N<sub>3</sub>), 61.0 (CH-triazole), 53.7, 53.3 (C<sub>sec</sub>-N<sub>3</sub>, C<sub>prim</sub>-N<sub>3</sub>), 51.2 (CH<sub>2</sub>-triazole), 38.3 (t, <sup>1</sup>J<sub>CP</sub> = 123.1 Hz, CH<sub>2</sub>CHP<sub>2</sub>), 21.1 (CH<sub>2</sub>CHP<sub>2</sub>) ppm. <sup>31</sup>P-NMR (162 MHz, D<sub>2</sub>O,  $\delta$ ): 18.9 ppm. IR (dry film):  $\nu_{\text{max}} = 3365 \text{ (s)}, 2872 \text{ (s)}, 2100 \text{ (s)}, 1729 \text{ (w)}, 1642 \text{ (w)}, 1454 \text{ (m)}, 1227 \text{ (w)}, 1058 \text{ (s)}, 919 \text{ (w)} \text{ cm}^{-1}$ .

### Low bisphosphonate-functionalized dendritic polyglycerol amine (dPGBP<sub>7%</sub>/NH<sub>2</sub>, dF = 10% (NH<sub>2</sub>), 7% (BP)) (6a)

The title compound was prepared from the azide-functionalized dPG bisphosphonate (**6**) ( $M_n = 8,150 \text{ g mol}^{-1}$ , dF = 10% (N<sub>3</sub>), 7% (BP)) according to the general procedure for reduction of azides and was obtained as a slightly brown solid.  $M_n =$

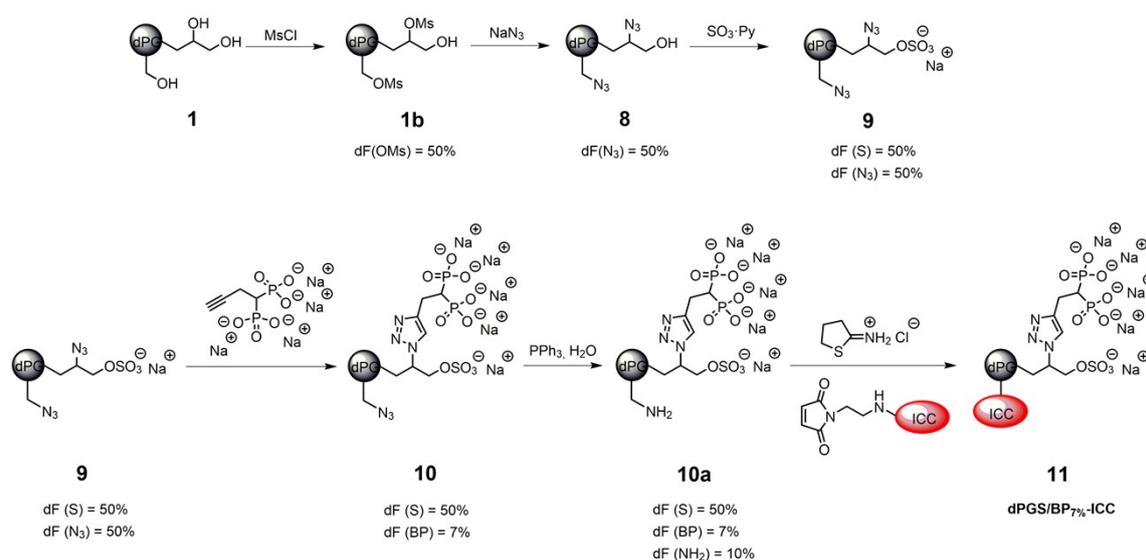
7,950 g mol<sup>-1</sup>, dF (NH<sub>2</sub>) = 10%, yield: 92%. <sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O, δ): 8.20 – 7.41 (m, 0.07H, triazole, NCH=C), 5.31 - 4.84 (m, 0.07H, CH-triazole), 4.75 – 4.31 (m, 0.14H, CH<sub>2</sub>N-triazole) 4.31 – 3.31 (m, 5H, dPG backbone), 3.31 – 3.09 (m, 0.14H, CH<sub>2</sub>CHP<sub>2</sub>), 2.63 – 2.18 (m, 0.07H, CH<sub>2</sub>CHP<sub>2</sub>) ppm. <sup>13</sup>C-NMR (176 MHz, D<sub>2</sub>O, δ): 146.8 (triazole, NCH=C), 124.8, 123.3 (triazole, NCH=C), 79.6, 79.4, 78.2, 77.9, 72.1, 70.9, 70.7, 70.4, 69.2, 68.9, 62.6 (dPG backbone), 60.8 (CH-triazole), 57.8, 52.8 (C<sub>sec</sub>.NH<sub>2</sub>, C<sub>prim</sub>.NH<sub>2</sub>), 51.5 (CH<sub>2</sub>-triazole), 39.3 (t, <sup>1</sup>J<sub>CP</sub> = 117.8 Hz, CH<sub>2</sub>CHP<sub>2</sub>), 21.7 (CH<sub>2</sub>CHP<sub>2</sub>) ppm. <sup>31</sup>P-NMR (162 MHz, D<sub>2</sub>O, δ): 19.4 ppm. IR (dry film): ν<sub>max</sub> = 3349 (s), 2873 (s), 2497 (w), 2357 (w), 1729 (w), 1632 (w), 1454 (m), 1324 (w), 1227 (w), 1052 (s), 922 (w), 882 (w), 678 (m) cm<sup>-1</sup>.

#### ICC-labeled low functionalized dendritic polyglycerol bisphosphonate (dPGBP<sub>7%</sub>-ICC) (7)

The title compound was prepared according to the general procedure for dye coupling using ICC-maleimide and low bisphosphonate-functionalized dendritic polyglycerol amine (**6a**). Freeze-drying gave the product as a pink solid. M<sub>n</sub> = 7,950 g mol<sup>-1</sup>, dye loading = 0.08, yield: 94%. UV-Vis (PBS): λ<sub>max</sub> = 553 nm.

#### 6S-ICG-labeled low functionalized dendritic polyglycerol bisphosphonate (dPGBP<sub>7%</sub>-6S-ICG) (7a)

The title compound was prepared according to the general procedure for dye coupling using 6S-ICG-maleimide and low bisphosphonate-functionalized dendritic polyglycerol amine (**6a**). Freeze-drying gave the product as a green solid. M<sub>n</sub> = 7,950 g mol<sup>-1</sup>, dye loading = 0.9, yield: 74%. UV-Vis (PBS): λ<sub>max</sub> = 785 nm.



**Fig. S4** Reaction pathway for the synthesis of half sulfated dPG azide (**9**) via mesylation (**1b**), azidation (**8**), and sulfation (**9**) and ICC-labeled dPGS/BP<sub>7%</sub> (**11**) via partial click coupling of the bisphosphonate alkyne to dPGS/N<sub>3</sub> (**10**), azide reduction (**10a**), and dye coupling (**11**) using 2-iminothiolane hydrochloride and ICC-maleimide.

#### Dendritic polyglycerol mesylate (dPGOMs, dF = 50%) (**1b**)

The title compound was prepared according to the general procedure for mesylation using 0.5 eq. mesyl chloride per OH group and was obtained as a honey-like brown oil. M<sub>n</sub> = 9,100 g mol<sup>-1</sup>, dF = 50%, yield: 78%. <sup>1</sup>H-NMR (400 MHz, acetone-D<sub>6</sub>, δ): 5.54 – 3.33 (m, 10H, dPG backbone), 3.18 (s, 3H, CH<sub>3</sub>, OMs) ppm. <sup>13</sup>C-NMR (176 MHz, acetone-D<sub>6</sub>, δ): 81.2, 79.5, 79.0, 78.2, 78.0, 73.8, 72.7, 72.4, 71.6, 71.3, 69.3 (dPG backbone), 38.9, 37.5 (OMs) IR (dry film): ν<sub>max</sub> = 3418 (m), 3025 (w), 2933 (m), 2879 (m), 1636 (w), 1460 (m), 1414 (w), 1337 (s) 1256 (w), 1168 (s), 1088 (s), 966 (s), 924 (s), 820 (s), 745 (m), 683 (m) cm<sup>-1</sup>.

#### Dendritic polyglycerol azide (dPGN<sub>3</sub>, dF = 50%) (**8**)

The title compound was prepared according to the general procedure for azidation from dendritic polyglycerol mesylate (**1b**) (M<sub>n</sub> = 9,100 g mol<sup>-1</sup>, dF = 50% (OMs)) and was obtained as a honey-like brown oil. M<sub>n</sub> = 7,000 g mol<sup>-1</sup>, dF = 50%, yield: 93%. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, δ): 4.70 – 3.06 (m, dPG backbone) ppm. <sup>13</sup>C-NMR (176 MHz, CDCl<sub>3</sub>, δ): 78.7, 73.0, 72.8, 71.3, 71.0, 69.9, 69.5 (dPG backbone), 63.7, 62.5, 61.9, 60.7, 60.5, 53.4, 51.8, 51.5 (C<sub>sec</sub>.N<sub>3</sub>, C<sub>prim</sub>.N<sub>3</sub>) IR (dry film): ν<sub>max</sub> = 3392 (m), 2904 (m), 2872 (m), 2517 (w), 2093 (s), 1799 (w), 1634 (w), 1450 (m), 1269 (s), 1080 (s), 932 (s), 858 (m), 753 (m), 663 (m) cm<sup>-1</sup>.

#### Half sulfated dendritic polyglycerol azide (dPGS/N<sub>3</sub>, dF = 50% (N<sub>3</sub>), 50% (S)) (**9**)

The title compound was prepared according to the literature by reacting dendritic polyglycerol azide (**8**) (M<sub>n</sub> = 7,000 g mol<sup>-1</sup>, dF = 50% (N<sub>3</sub>)) with SO<sub>3</sub> pyridine complex in anhydrous DMF.<sup>3, 4</sup> Freeze-drying yielded the product as a slightly brown solid. M<sub>n</sub> = 11,250 g mol<sup>-1</sup>, dF (S) = 50%, yield: 76%. <sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O, δ): 4.74 – 4.50 (m, 1H, C<sub>sec</sub>.HOSO<sub>3</sub>), 4.50 – 4.10 (m, 2H, C<sub>prim</sub>.H<sub>2</sub>OSO<sub>3</sub>), 4.10 – 3.22 (m, 10H, dPG backbone) ppm. <sup>13</sup>C-NMR (176 MHz, D<sub>2</sub>O, δ): 78.3, 76.8, 75.9 (C<sub>sec</sub>.HOSO<sub>3</sub>,

$C_{\text{prim.H}_2\text{OSO}_3}$ , 70.8, 70.0, 68.7, 67.6, 66.8 (dPG backbone), 60.8, 60.6, 51.3, 50.9 ( $C_{\text{sec.N}_3}$ ,  $C_{\text{prim.N}_3}$ ) IR (dry film):  $\nu_{\text{max}} = 3456$  (w), 2919 (m), 2789 (m), 2101 (s), 1641 (w), 1459 (m), 1345 (w), 1226 (s), 1079 (s), 1036 (s), 933 (s), 776 (s)  $\text{cm}^{-1}$ .

### Bisphosphonate-functionalized dendritic polyglycerol sulfate (dPGS/BP<sub>7%</sub>, dF = 50% (S), 7% (BP)) (10)

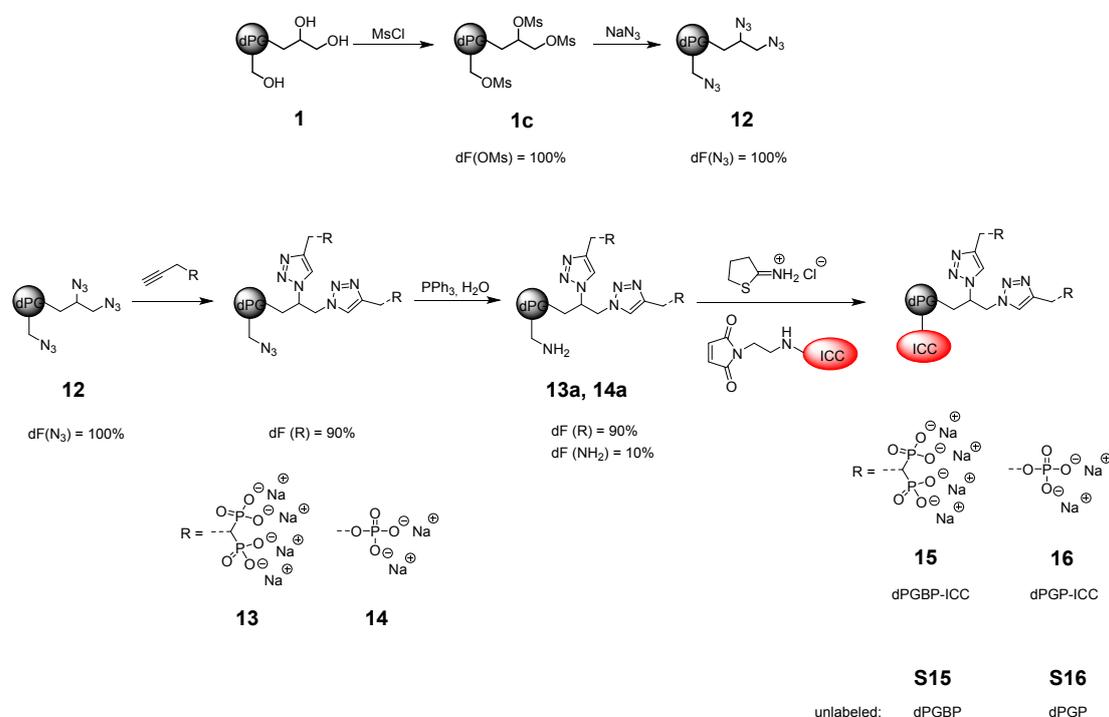
The title compound was prepared according to the general procedure for click coupling using azide-functionalized dendritic polyglycerol sulfate (9) ( $M_n = 11,250 \text{ g mol}^{-1}$ , dF = 50% ( $\text{N}_3$ ), 50% (S)) and 10 eq. of the bisphosphonate alkyne. Freeze-drying yielded the product as a slightly brown solid.  $M_n = 13,050 \text{ g mol}^{-1}$ , dF (BP) = 7%, yield: 77%.  $^1\text{H-NMR}$  (400 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 8.96 – 7.38 (m, 0.07H, triazole,  $\text{NCH=C}$ ), 5.49 – 4.93 (m, 0.07H,  $\text{CH-triazole}$ ), 4.70 – 3.39 (m, 5H,  $\text{CH}_2\text{N-triazole}$ ,  $C_{\text{sec.HOSO}_3}$ ,  $C_{\text{prim.H}_2\text{OSO}_3}$ , dPG backbone), 3.32 – 2.99 (m, 0.14H,  $\text{CH}_2\text{CHP}_2$ ), 2.54 – 2.18 (m, 0.07H,  $\text{CH}_2\text{CHP}_2$ ) ppm.  $^{13}\text{C-NMR}$  (176 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 147.1 (triazole,  $\text{NCH=C}$ ), 125.0, 123.5 (triazole,  $\text{NCH=C}$ ), 78.3, 76.8 ( $C_{\text{sec.HOSO}_3}$ ,  $C_{\text{prim.H}_2\text{OSO}_3}$ ), 72.3, 70.7, 70.0, 68.8, 67.6 (dPG backbone), 60.8 ( $\text{CH-triazole}$ ), 60.6, 57.5, 51.2 ( $C_{\text{sec.N}_3}$ ,  $C_{\text{prim.N}_3}$ ), 50.9 ( $\text{CH}_2\text{-triazole}$ ), 39.5 (t,  $^1J_{\text{CP}} = 117.1 \text{ Hz}$ ,  $\text{CH}_2\text{CHP}_2$ ), 21.8 ( $\text{CH}_2\text{CHP}_2$ ) ppm.  $^{31}\text{P-NMR}$  (162 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 19.6 ppm. IR (dry film):  $\nu_{\text{max}} = 3417$  (m), 2881 (m), 2357 (w), 2102 (s), 1633 (m), 1453 (m), 1227 (s), 1071 (s), 1041 (s), 930 (s), 776 (s)  $\text{cm}^{-1}$ .

### Amine- and bisphosphonate-functionalized dendritic polyglycerol sulfate (dPGS/BP<sub>7%</sub>/NH<sub>2</sub>, dF = 10% (NH<sub>2</sub>), 50% (S), 7% (BP)) (10a)

The title compound was prepared from bisphosphonate-functionalized dendritic polyglycerol sulfate (10) ( $M_n = 13,050 \text{ g mol}^{-1}$ , dF = 43% ( $\text{N}_3$ ), 50% (S), 7% (BP)) according to the general procedure for reduction of azides and was obtained as a slightly brown solid.  $M_n = 12,850 \text{ g mol}^{-1}$ , dF ( $\text{NH}_2$ ) = 10%, yield: 97%.  $^1\text{H-NMR}$  (400 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 8.98 – 7.80 (m, 0.07H, triazole,  $\text{NCH=C}$ ), 5.51 – 5.13 (m, 0.07H,  $\text{CH-triazole}$ ), 4.70 – 3.40 (m, 5H,  $\text{CH}_2\text{N-triazole}$ ,  $C_{\text{sec.HOSO}_3}$ ,  $C_{\text{prim.H}_2\text{OSO}_3}$ , dPG backbone), 3.33 – 3.06 (m, 0.14H,  $\text{CH}_2\text{CHP}_2$ ), 2.53 – 2.29 (m, 0.07H,  $\text{CH}_2\text{CHP}_2$ ) ppm.  $^{13}\text{C-NMR}$  (176 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 147.3 (triazole,  $\text{NCH=C}$ ), 125.1, 123.4 (triazole,  $\text{NCH=C}$ ), 78.3, 76.9 ( $C_{\text{sec.HOSO}_3}$ ,  $C_{\text{prim.H}_2\text{OSO}_3}$ ), 70.7, 70.0, 68.7, 67.7 (dPG backbone), 60.7, 57.5 ( $\text{CH-triazole}$ ), 51.4, 50.9 ( $\text{CH}_2\text{-triazole}$ ), 39.5 (t,  $^1J_{\text{CP}} = 117.3 \text{ Hz}$ ,  $\text{CH}_2\text{CHP}_2$ ), 21.8 ( $\text{CH}_2\text{CHP}_2$ ) ppm.  $^{31}\text{P-NMR}$  (162 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 19.8 ppm. IR (dry film):  $\nu_{\text{max}} = 3438$  (m), 2924, 2879 (m), 2308 (w), 2103 (s), 1635 (m), 1455 (m), 1401 (w), 133 (w), 1226 (s), 1074 (s), 1038 (s), 930 (s), 776 (s)  $\text{cm}^{-1}$ .

### ICC-labeled bisphosphonate-functionalized dendritic polyglycerol sulfate (dPGS/BP<sub>7%</sub>-ICC) (11)

The title compound was prepared according to the general procedure for dye coupling using ICC-maleimide and amine-functionalized bisphosphonated dendritic polyglycerol sulfate (10a). Freeze-drying gave the product as a pink solid.  $M_n = 12,850 \text{ g mol}^{-1}$ , dye loading = 0.15, yield: 74%. UV-Vis (PBS):  $\lambda_{\text{max}} = 559 \text{ nm}$ .



**Fig. S5** Reaction pathway for the synthesis of ICC-labeled dPGBP (15) and dPGP (16) via mesylation (1c), azidation (12), click coupling of the respective alkyne (13, 14), reduction of the azide (13a, 14a), and dye coupling using 2-iminothiolane hydrochloride and ICC-maleimide. Unlabeled dPGBP (S15) and dPGP (S16) were prepared by full conversion of dPG azide (12) via click-reaction using the respective alkyne precursor.

### Dendritic polyglycerol mesylate (dF = 100%) (1c)

The title compound was prepared according to the general procedure for mesylation using 1.1 eq. mesyl chloride per OH group and was obtained as a honey-like brown oil.  $M_n = 12,300 \text{ g mol}^{-1}$ , dF = 100%, yield: 65%.  $^1\text{H-NMR}$  (400 MHz, Acetone- $D_6$ ,  $\delta$ ): 5.16 - 3.42 (m, 5H, dPG-backbone) 3.16 (s, 3H,  $\text{CH}_3$ , OMs) ppm.

### Dendritic polyglycerol azide (dF = 100%) (12)

The title compound was prepared according to the general procedure for azidation from dendritic polyglycerol mesylate (1c) ( $M_n = 12,300 \text{ g mol}^{-1}$ , dF = 100% (OMs)) and was obtained as a honey-like brown oil.  $M_n = 8,000 \text{ g mol}^{-1}$ , dF = 100%, yield: 100%.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 4.30 – 2.87 (m, dPG backbone) ppm.

### Highly bisphosphonate-functionalized dendritic polyglycerol azide (dF = 10% ( $\text{N}_3$ ), 90% (BP)) (13)

The title compound was prepared according to the general procedure for click coupling using dendritic polyglycerol azide (12) ( $M_n = 8,000 \text{ g mol}^{-1}$ , dF = 100% ( $\text{N}_3$ )) and 0.9 eq. of the bisphosphonate-functionalized alkyne per  $\text{N}_3$  group. Freeze-drying yielded the product as a colorless solid.  $M_n = 30,050 \text{ g mol}^{-1}$ , dF (BP) = 90%, yield: 89%.  $^1\text{H-NMR}$  (400 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 8.26 – 7.05 (m, 1H, triazole,  $\text{NCH}=\text{C}$ ), 5.43 – 4.39 (m, 4H,  $\text{CH}$ -triazole,  $\text{CH}_2\text{N}$ -triazole, dPG backbone) 4.39 – 3.22 (m, 4.5H, dPG backbone), 3.22 – 2.79 (m, 2H,  $\text{CH}_2\text{CHP}_2$ ), 2.79 – 1.97 (m, 1H,  $\text{CH}_2\text{CHP}_2$ ) ppm.  $^{13}\text{C-NMR}$  (176 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 146.2 (triazole,  $\text{NCH}=\text{C}$ ), 124.7, 123.8 (triazole,  $\text{NCH}=\text{C}$ ), 78.2, 78.0, 70.3, 69.4, 68.5, 61.7 (dPG backbone), 60.8 ( $\text{CH}$ -triazole), 50.6 ( $\text{CH}_2$ -triazole), 38.7 (t,  $^1J_{\text{CP}} = 118.2 \text{ Hz}$ ,  $\text{CH}_2\text{CHP}_2$ ), 21.5 ( $\text{CH}_2\text{CHP}_2$ ) ppm.  $^{31}\text{P-NMR}$  (162 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 20.2 ppm. IR (dry film):  $\nu_{\text{max}} = 3358 \text{ (s)}$ , 2871 (s), 2198 (w), 1636 (w), 1455 (m), 1266 (w), 1061 (s), 927 (m), 873 (m)  $\text{cm}^{-1}$ .

### Highly bisphosphonate-functionalized dendritic polyglycerol amine (dF = 10% ( $\text{NH}_2$ ), 90% (BP)) (13a)

The title compound was prepared from the azide-functionalized dPG bisphosphonate (13) ( $M_n = 30,050 \text{ g mol}^{-1}$ , dF = 10% ( $\text{N}_3$ ), 90% (BP)) according to the general procedure for reduction of azides and was obtained as a colorless solid.  $M_n = 29,850 \text{ g mol}^{-1}$ , dF ( $\text{NH}_2$ ) = 10%, yield: 84%.  $^1\text{H-NMR}$  (400 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 8.34 – 7.35 (m, 1H, triazole,  $\text{NCH}=\text{C}$ ), 5.52 – 4.41 (m, 4H,  $\text{CH}$ -triazole,  $\text{CH}_2\text{N}$ -triazole, dPG backbone) 4.41 – 3.13 (m, 5H, dPG backbone), 3.13 – 2.76 (m, 2H,  $\text{CH}_2\text{CHP}_2$ ), 2.76 – 2.14 (m, 1H,  $\text{CH}_2\text{CHP}_2$ ) ppm.  $^{13}\text{C-NMR}$  (176 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 146.2 (triazole,  $\text{NCH}=\text{C}$ ), 124.7, 123.8 (triazole,  $\text{NCH}=\text{C}$ ), 78.2, 70.3, 69.4, 68.5, 61.7 (dPG backbone), 60.8 ( $\text{CH}$ -triazole), 50.6 ( $\text{CH}_2$ -triazole), 38.8 (t,  $^1J_{\text{CP}} = 118.4 \text{ Hz}$ ,  $\text{CH}_2\text{CHP}_2$ ), 21.5 ( $\text{CH}_2\text{CHP}_2$ ) ppm.  $^{31}\text{P-NMR}$  (162 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 20.1 ppm. IR (dry film):  $\nu_{\text{max}} = 3351 \text{ (s)}$ , 2924 (w), 2386 (w), 2289 (w), 1648 (m), 1553 (m), 1445 (m), 1382 (w), 1319 (w), 1149 (m), 1125 (m), 1051 (s), 946 (w), 876 (s)  $\text{cm}^{-1}$ .

### ICC-labeled highly functionalized dendritic polyglycerol bisphosphonate (dPGBP-ICC) (15)

The title compound was prepared according to the general procedure for dye coupling using ICC-maleimide and highly bisphosphonate-functionalized dendritic polyglycerol amine (13a). Freeze-drying gave the product as a pink solid.  $M_n = 29,850 \text{ g mol}^{-1}$ , dye loading = 0.39, yield: 75%. UV-Vis (PBS):  $\lambda_{\text{max}} = 553 \text{ nm}$ .

### Azide-functionalized dendritic polyglycerol phosphate (dF = 10% ( $\text{N}_3$ ), 90% (P)) (14)

The title compound was prepared according to the general procedure for click coupling using dendritic polyglycerol azide (12) ( $M_n = 8,000 \text{ g mol}^{-1}$ , dF = 100% ( $\text{N}_3$ )) and 0.9 eq. of the phosphate-functionalized alkyne per  $\text{N}_3$  group. Freeze-drying yielded the product as a slightly brown solid.  $M_n = 21,150 \text{ g mol}^{-1}$ , dF (P) = 90%, yield: 72%.  $^1\text{H-NMR}$  (400 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 8.32 – 7.51 (m, 1H, triazole,  $\text{NCH}=\text{C}$ ), 5.47 – 4.82 (m, 3H,  $\text{CH}$ -triazole,  $\text{CH}_2\text{N}$ -triazole) 4.76 – 2.77 (m, 5H, dPG backbone) ppm.  $^{13}\text{C-NMR}$  (176 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 144.7 (triazole,  $\text{NCH}=\text{C}$ ), 125.2, 124.4, 124.1 (triazole,  $\text{NCH}=\text{C}$ ), 78.3, 77.7, 71.2, 69.5, 68.4 (dPG backbone), 61.0 ( $\text{CH}$ -triazole), 57.8 ( $\text{CH}_2\text{OPO}_3$ ), 51.2, 50.5 ( $\text{CH}_2$ -triazole) ppm.  $^{31}\text{P-NMR}$  (162 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 2.6 ppm. IR (dry film):  $\nu_{\text{max}} = 3360 \text{ (m)}$ , 3139 (w), 2942 (w), 2882 (w), 2358 (w), 2317 (w), 2101 (w), 1648 (m), 1557 (m), 1461 (m), 1356 (m), 1103 (s), 1048 (s), 983 (s), 917 (s), 826 (s)  $\text{cm}^{-1}$ .

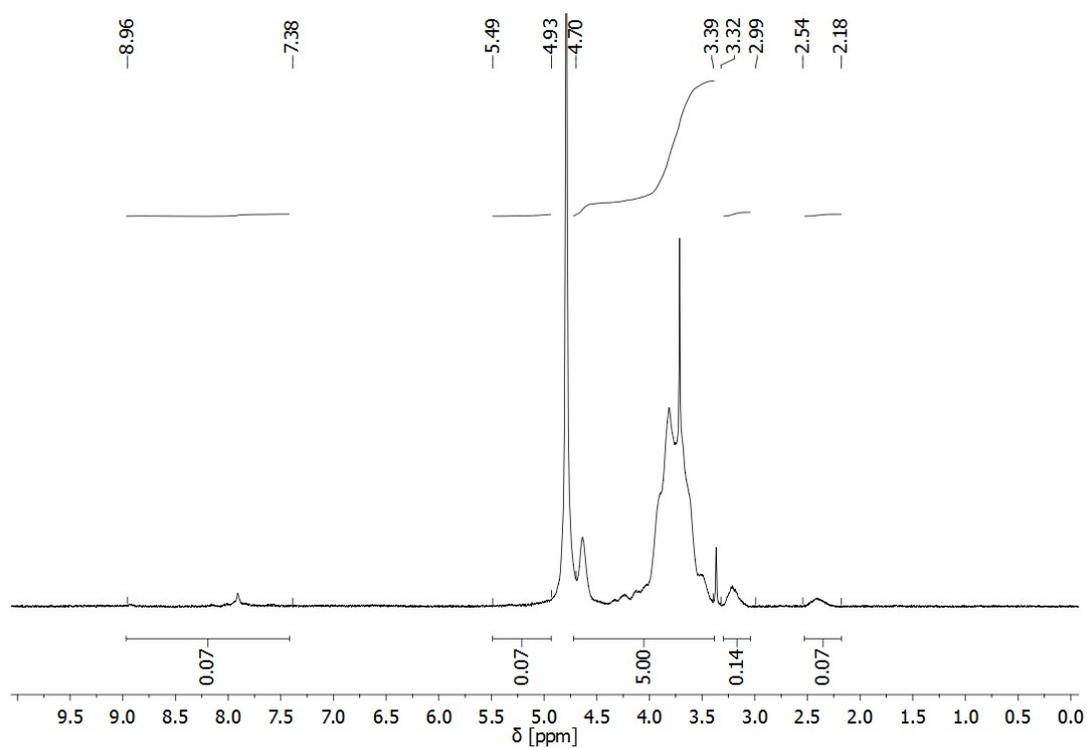
### Amine-functionalized dendritic polyglycerol phosphate (dF = 10% ( $\text{NH}_2$ ), 90% (P)) (14a)

The title compound was prepared from azide-functionalized dPG phosphate (14) ( $M_n = 21,150 \text{ g mol}^{-1}$ , dF = 10% ( $\text{N}_3$ ), 90% (P)) according to the general procedure for reduction of azides and was obtained as a slightly brown solid.  $M_n = 20,950 \text{ g mol}^{-1}$ , dF ( $\text{NH}_2$ ) = 10%, yield: 88%.  $^1\text{H-NMR}$  (400 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 8.29 – 7.37 (m, 1H, triazole,  $\text{NCH}=\text{C}$ ), 5.53 – 4.82 (m, 3H,  $\text{CH}$ -triazole,  $\text{CH}_2\text{N}$ -triazole, dPG backbone) 4.64 – 2.39 (m, 5H, dPG backbone) ppm.  $^{13}\text{C-NMR}$  (176 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 144.3 (triazole,  $\text{NCH}=\text{C}$ ), 125.3, 124.5 (triazole,  $\text{NCH}=\text{C}$ ), 78.3, 77.7, 71.1, 70.2, 69.2, 68.2 (dPG backbone), 61.0 ( $\text{CH}$ -triazole), 58.1 ( $\text{CH}_2\text{OPO}_3$ ), 51.3, 50.6 ( $\text{CH}_2$ -triazole) ppm.  $^{31}\text{P-NMR}$  (162 MHz,  $\text{D}_2\text{O}$ ,  $\delta$ ): 0.7 ppm. IR (dry film):  $\nu_{\text{max}} = 3392 \text{ (s)}$ , 3146 (w), 2952 (w), 2885 (w), 2323 (w), 1647 (m), 1561 (w), 1460 (m), 1358 (w), 1222 (w), 1178 (w), 1149 (w), 1043 (s), 1013 (s), 927 (s), 825 (m)  $\text{cm}^{-1}$ .

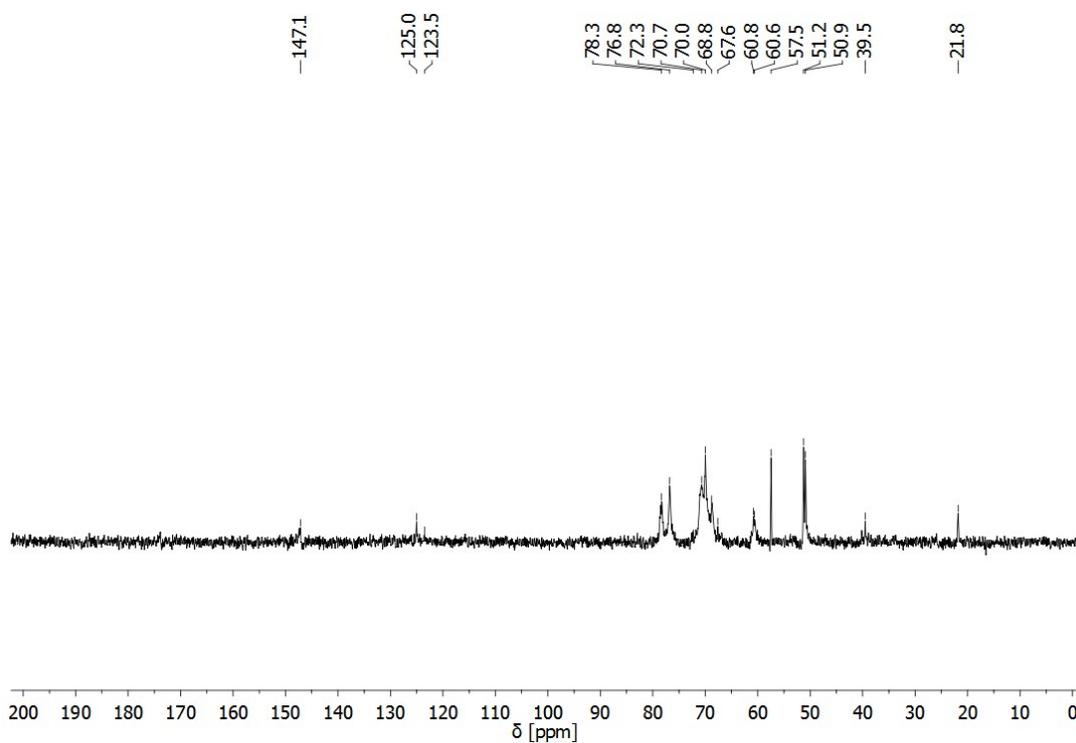
### ICC-labeled dendritic polyglycerol phosphate (dPGP-ICC) (16)

The title compound was prepared according to the general procedure for dye coupling using ICC-maleimide and amine-functionalized dendritic polyglycerol phosphate (14a). Freeze-drying gave the product as a pink solid.  $M_n = 20,950 \text{ g mol}^{-1}$ , dye loading = 0.12, yield: 88%. UV-Vis (PBS):  $\lambda_{\text{max}} = 553 \text{ nm}$ .

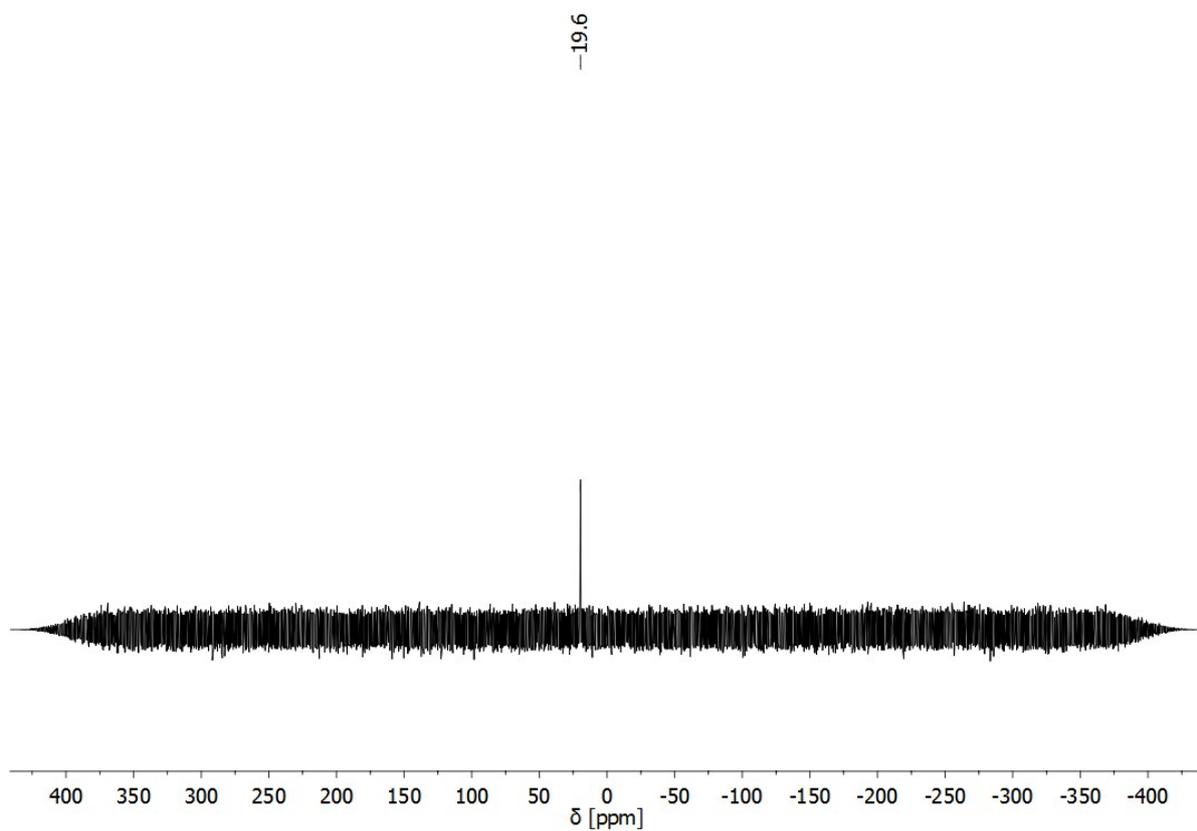
## Analytical Data



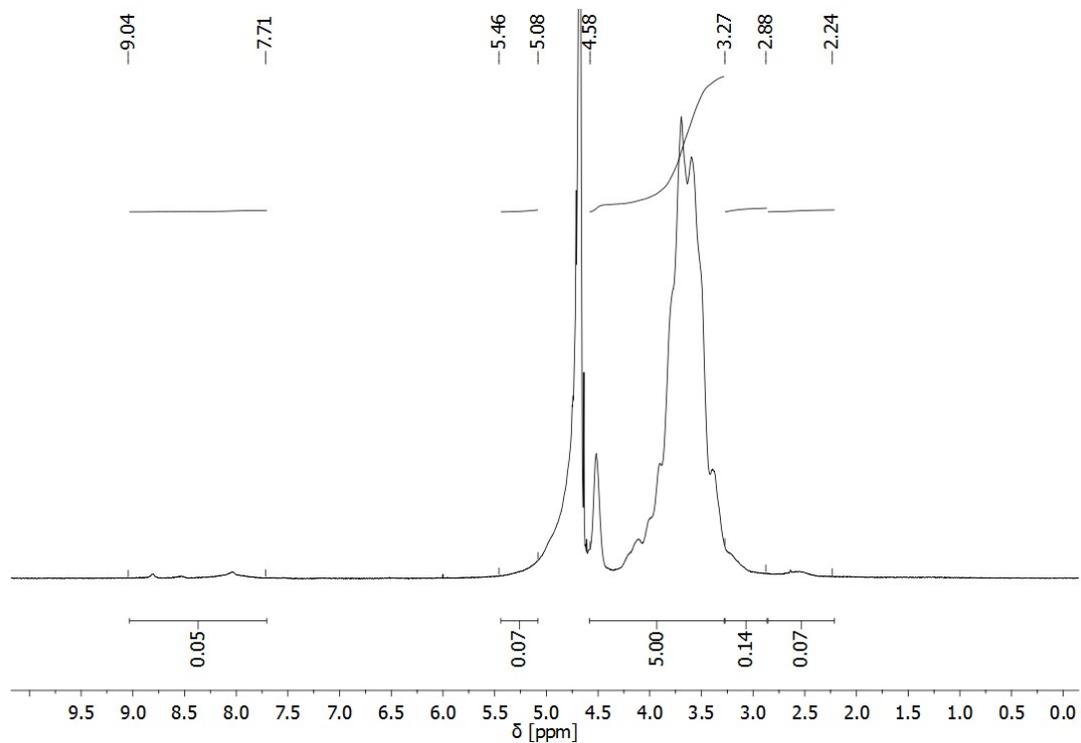
**Fig. S6**  $^1\text{H-NMR}$  spectra (400 MHz,  $\text{D}_2\text{O}$ ) of dPGS/BP<sub>7%</sub> (**10**).



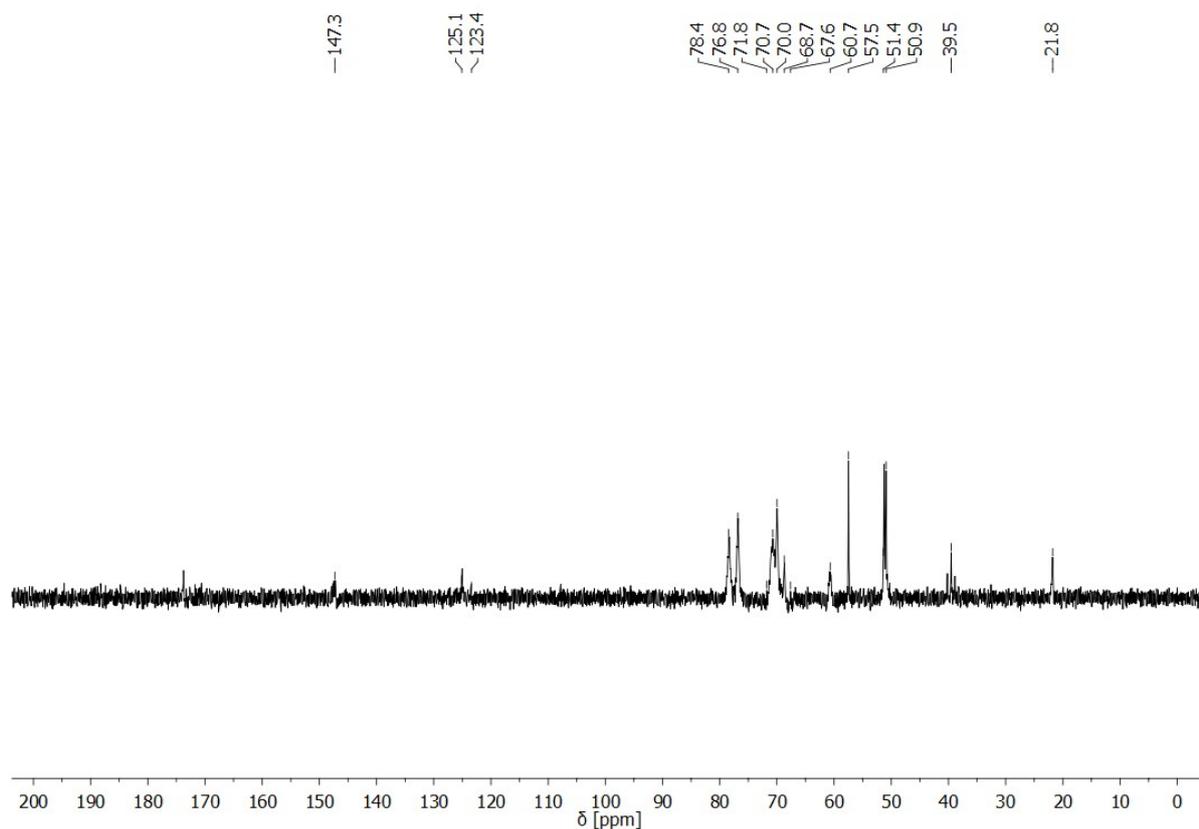
**Fig. S7**  $^{13}\text{C-NMR}$  spectra (176 MHz,  $\text{D}_2\text{O}$ ) of dPGS/BP<sub>7%</sub> (**10**).



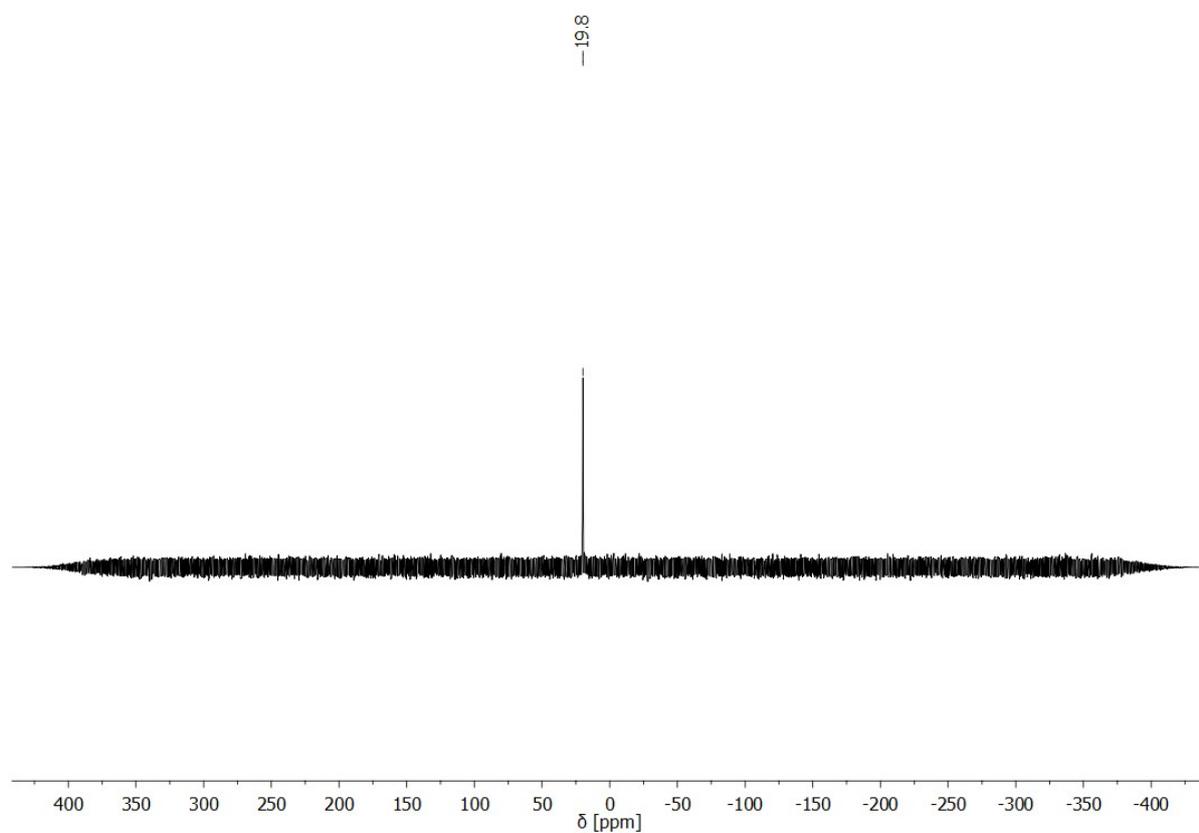
**Fig. S8**  $^{31}\text{P}$ -NMR spectra (101 MHz,  $\text{D}_2\text{O}$ ) of dPGS/BP<sub>7%</sub> (**10**).



**Fig. S9**  $^1\text{H}$ -NMR spectra (400 MHz,  $\text{D}_2\text{O}$ ) of dPGS/BP<sub>7%</sub>/NH<sub>2</sub> (**10a**).



**Fig. S10**  $^{13}\text{C}$ -NMR spectra (176 MHz,  $\text{D}_2\text{O}$ ) of dPGS/BP<sub>7%</sub>/NH<sub>2</sub> (**10a**).



**Fig. S11**  $^{31}\text{P}$ -NMR spectra (400 MHz,  $\text{D}_2\text{O}$ ) of dPGS/BP<sub>7%</sub>/NH<sub>2</sub> (**10a**).

**Table S1** Specification of the dye-labeled dPG derivatives.

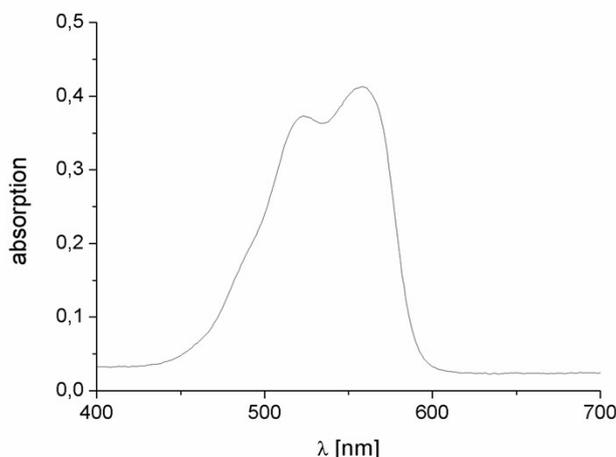
Polymer	#	$M_n^a$ [g mol <sup>-1</sup> ]	NF <sup>b)</sup>	dF <sup>c)</sup> [%]	ICC-loading <sup>d)</sup> [dye/ polymer]
dPG-ICC	3	6,150	-	-	0.09
dPGS-ICC	5	14,000	67	83	0.17
dPGBP <sub>7%</sub> -ICC	7	7,950	6	7	0.08
dPGS/BP <sub>7%</sub> -ICC	11	12,850	41 S/ 6 BP	50% S/ 7% BP	0.15
dPGBP-ICC	15	29,850	73	90	0.19
dPGP-ICC	16	20,950	73	90	0.12

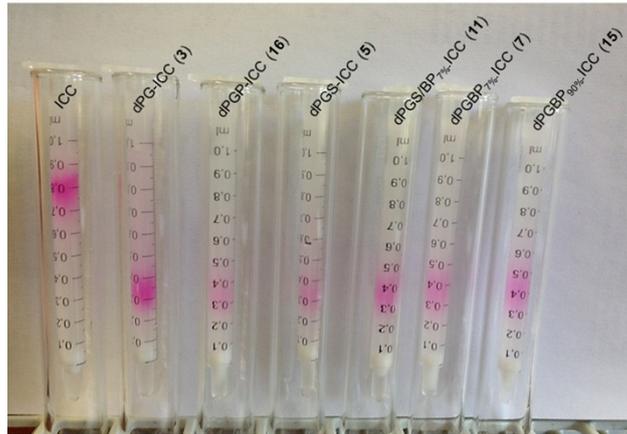
<sup>a)</sup> Number average molecular weight calculated from the dF. <sup>b)</sup> Number of functional groups per polymer. <sup>c)</sup> Degree of functionalization determined by <sup>1</sup>H-NMR or elemental analysis. <sup>d)</sup> Average number of dye molecule per polymer determined by UV-Vis spectroscopy.

**Table S2** Specification of the dPG polyanions derived from dendritic polyglycerol.

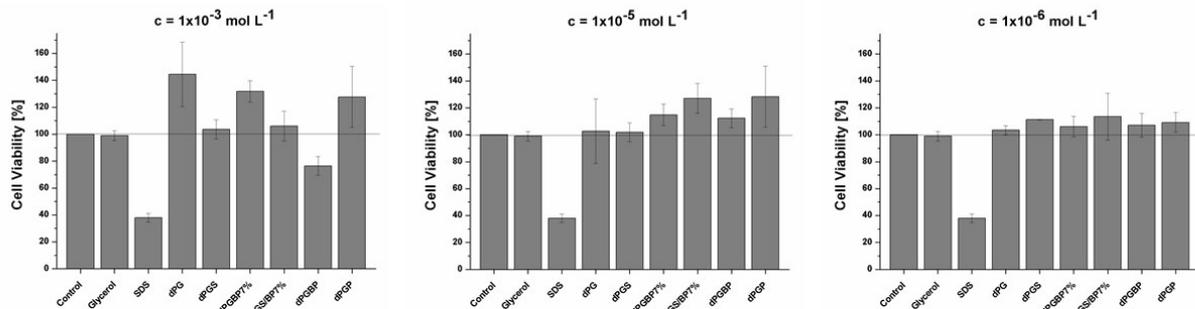
Polymer	#	$M_n^a$ [g mol <sup>-1</sup> ]	NF <sup>b)</sup>	dF <sup>c)</sup> [%]	$d_n \pm SD^d$ [nm]	PDI <sup>e)</sup>	$\zeta$ -potential $\pm SD^f$ [mV]
dPG	1	6,000	81	-	4 ± 1	0.23	-
dPGS	S5	12,500	63	78	7 ± 1	0.27	-20 ± 4
dPGBP <sub>7%</sub>	6	8,150	6	7	7 ± 1	0.25	-13 ± 3
dPGS/BP <sub>7%</sub>	10	13,050	41 (S) 6 (BP)	50 (S) 7 (BP)	8 ± 1	0.27	-21 ± 4
dPGBP	S15	36,750	81	100	8 ± 1	0.24	-27 ± 3
dPGP	S16	26,880	81	100	7 ± 1	0.29	-24 ± 4

<sup>a)</sup> Number average molecular weight calculated from the dF. <sup>b)</sup> Number of functional groups per polymer. <sup>c)</sup> Degree of functionalization determined by <sup>1</sup>H-NMR or elemental analysis. <sup>d)</sup> Hydrodynamic diameter (mean ± standard deviation (SD)) by DLS in PBS (pH 7.4) from the size distribution by volume. <sup>e)</sup> Polydispersity index (DLS). <sup>f)</sup>  $\zeta$ -potential (mean ± SD) in 10 mM phosphate buffer (pH 7.4).

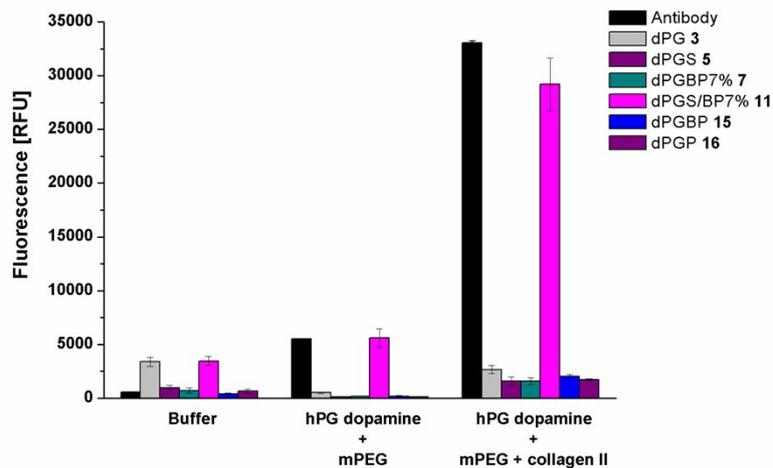
**Fig. S12** Representative UV-Vis absorption spectra of dPGS/BP<sub>7%</sub>-ICC (**11**). The spectra of the other ICC-labeled dPG derivatives look similar.



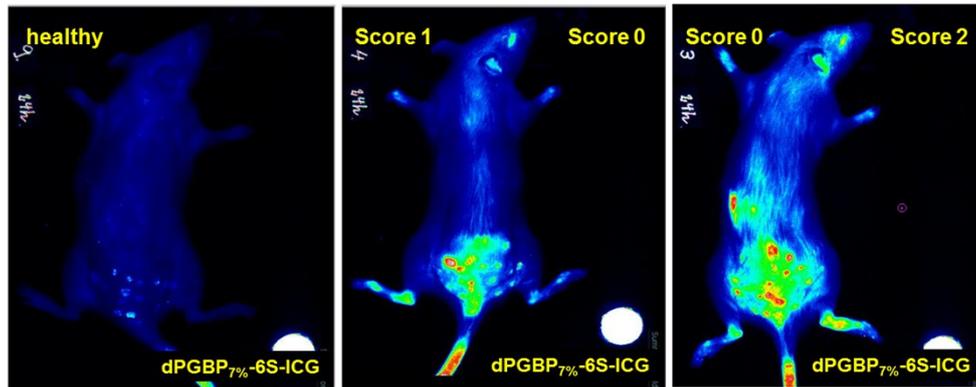
**Fig. S13** Size exclusion chromatography (SEC) of ICC-labeled dPG derivatives **3**, **5**, **7**, **11**, **15**, and **16** in water using Sephadex™ G25 superfine. No free dye was left in the ICC-conjugates.



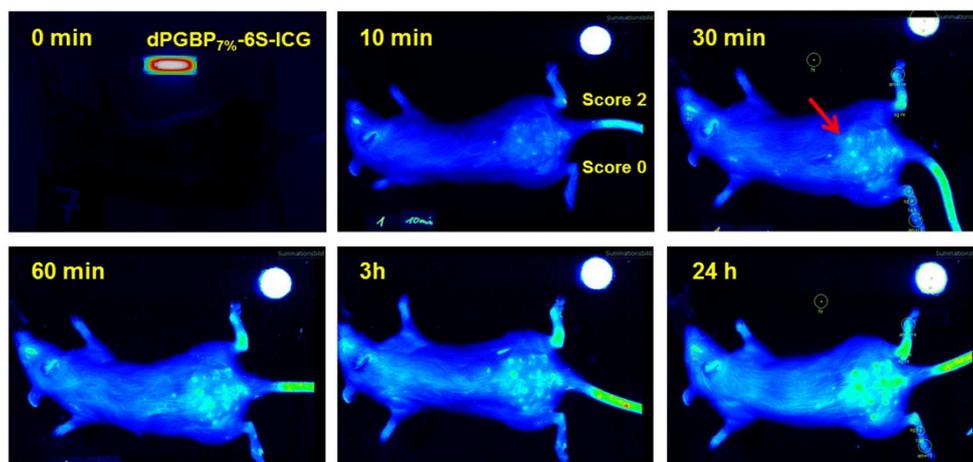
**Fig. S14** Metabolic activity of human chondrocytes 24 h after incubation with non-labeled anionic dPG derivatives at a concentration of  $10^{-3}$ ,  $10^{-5}$ , and  $10^{-6} \text{ mol L}^{-1}$  reflecting the compound cytotoxicity. Cell viability was determined by applying an alamarBlue assay. Glycerol was used as a positive, sodium dodecyl sulfate (SDS) as a negative control. The standard deviation of untreated cells and three independent experiments is represented by error bars.



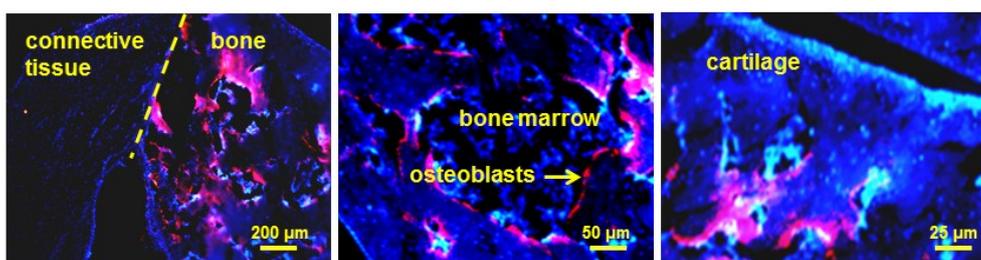
**Fig. S15** Collagen type II binding assay. Affinity of ICC-labeled collagen II antibody and dPG anions to the non-functionalized well plate (buffer), blocked surface (hPG dopamine + mPEG), and collagen II-functionalized well plate after incubation over 1 h at room temperature (antibody) or 24 h at  $37^\circ\text{C}$  (dPG polymers) as determined by the fluorescence intensity from three independent measurements.



**Fig. S16** Near infrared images of healthy rats and animals with collagen-induced rheumatoid arthritis showing different scores, 24 h after intravenous injection of dPGBP<sub>7%</sub>-6S-ICG (7a).



**Fig. S17** Near infrared images of time-dependent accumulation of dPGBP<sub>7%</sub>-6S-ICG (7a) in rats with collagen-induced rheumatoid arthritis showing score 2 and score 0. The red arrow indicates sites of injection.

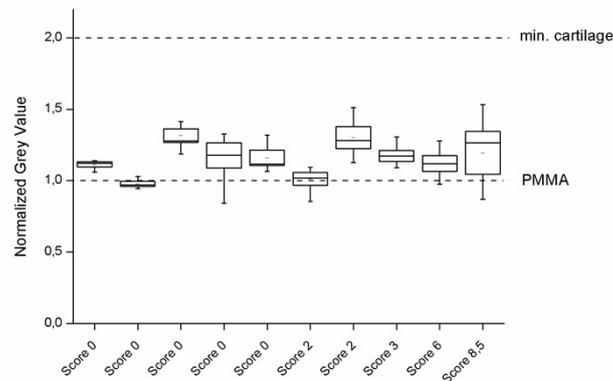


**Fig. S18** Fluorescence microscopy images of tissue slides from tibiotarsal articulations of rats with collagen-induced rheumatoid arthritis (CIA) showing a score 0. Images were taken 3 h after intravenous injection of ICC-labeled dPGBP<sub>7%</sub> (7). dPGBP<sub>7%</sub>-ICC accumulates only in bone and is uptaken by osteoblasts.

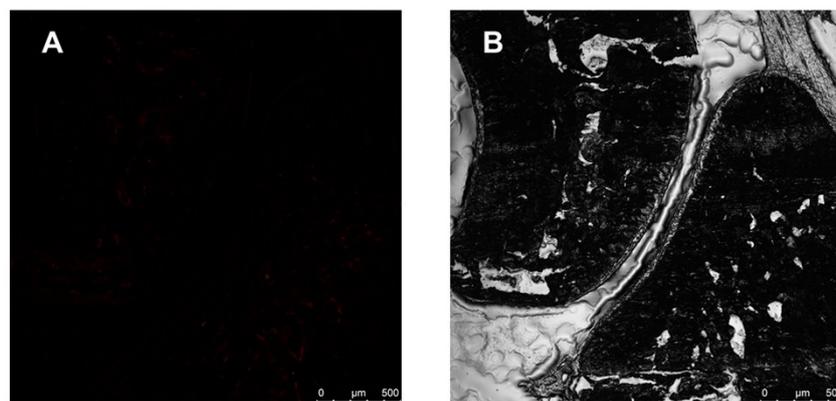
### Calcification of cartilage in rheumatoid arthritis

Examination of cartilage calcification within rheumatoid arthritis was accomplished and processed in ImageJ (U. S. National Institutes of Health, Bethesda, Maryland, USA). Hereto grey values of the poly(methyl methacrylate) (PMMA) matrix, the mineralized, and non-mineralized cartilage were determined from ten independent spots throughout the CIA joints. Areas around cell lacunas were avoided as they showed darker patches than the rest of the respective tissue. Since the CIA score does not affect the grey scale of the embedding medium, PMMA was used as reference for non-calcified material and its average grey value was set to 1.0. Compared to bone, mineralized cartilage is more homogenous in color. Therefore, it served as reference for calcified material and its average grey level was set to 2.0. Grey values of non-mineralized cartilage should

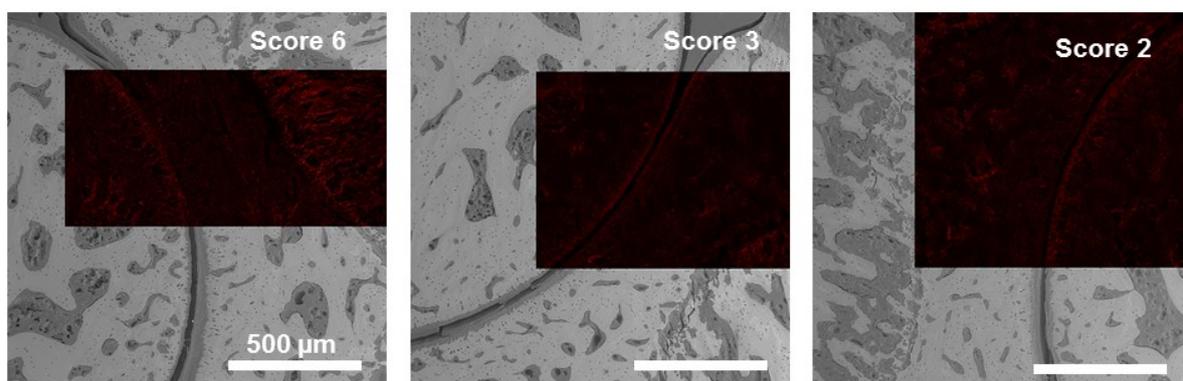
ideally lay in-between but few outliers were found (**Fig. S19**). Nevertheless, no significant differences in the grey scales between the CIA scores were observed, indicating that mineralization of cartilage did not occur over the course of rheumatoid arthritis.



**Fig. S19** Normalized grey values of articular cartilage from joints showing different CIA scores. PMMA was used as a reference for non-calcified material and mineralized cartilage as a reference for calcified material.



**Fig. S20** Confocal laser scanning microscopy (CLSM) images of an untreated CIA rat joint embedded in PMMA with a score 0. (A) Dark field fluorescence signal. (B) Bright field image of the joint. A minor fluorescence signal was observed due to autofluorescence of the tissue. The same fluorescence intensity was used for all other probes.



**Fig. S21** Superimposed images taken by confocal laser scanning microscopy (CLSM) (red) and scanning electron microscopy (SEM) (grey) of CIA rat joints with different scores embedded in PMMA. Rats were treated once with ICC-labeled dPGBP<sub>7%</sub> (**7**) prior to ex vivo imaging of tibiotarsal articulations along the longitudinal-sagittal plane. Feet were removed 3 h p.i. and stored at -80 °C in Tissue Tek until further usage.

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