**Supplementary information to:**

**Improved evaluation of antivascular cancer therapy using constrained tracer-kinetic modeling for multi-agent dynamic contrast-enhanced MRI**

**Supplementary Information 1: Dendrimer synthesis and characterization**

*Materials*. All reagents, chemicals, materials and solvents were obtained from commercial sources, and were used as received: Biosolve, Merck and Cambridge Isotope Laboratories for (deuterated) solvents; Aldrich, Acros, ABCR, Merck and Fluka for chemicals, materials and reagents. DOTA-NHS ester was purchased from Macrocyclics or CheMatech. The G2-PPI-(NH2)8 and G5-PPI-(NH2)64 starting materials are amine terminated poly(propylene imine) (PPI) dendrimers ([1](#_ENREF_1)), and were acquired from SyMO-Chem BV, Eindhoven, the Netherlands. The molecular structure of G2-PPI-(NH2)8 is shown in Supplementary Figure S1. All solvents were of AR quality. Moisture or oxygen-sensitive reactions were performed under an Ar atmosphere. Sephadex G-25 and PD-10 columns were obtained from GE Healthcare.

*Methods*. 1H-NMR, 13C-NMR spectra were recorded on a Varian Mercury (400 MHz for 1H-NMR and 100 MHz for 13C-NMR) spectrometer at 298 K. Chemical shifts are reported in ppm downfield from TMS at r.t. using deuterated chloroform (CDCl3) as a solvent and internal standard unless otherwise indicated. Abbreviations used for splitting patterns are s = singlet, t = triplet, q = quartet, m = multiplet and br = broad. Infrared (IR) spectra were recorded on a Perkin Elmer 1600 FT-IR (UATR). Preparative size exclusion chromatography was performed using Sephadex G-25 or Pd10 using water as eluent. Liquid Chromatography Electrospray Ionization Mass Spectrometry (LC-ESI-MS) was performed using a Shimadzu LC-10 AD VP series HPLC coupled to a diode array detector (Finnigan Surveyor PDA Plus detector, Thermo Electron Corporation) and an Ion-Trap (LCQ Fleet, Thermo Scientific) where ions were created via electrospray ionization (ESI). LC-analyses (on **1** and precursors to **1**) were performed using an Alltech Alltima HP C18 3μ column using an injection volume of 1-4 μL, a flow rate of 0.2 mL min-1 and typically a gradient (5% to 100% in 10 min, held at 100% for a further 3 min) of CH3CN in H2O (both containing 0.1% formic acid) at 298 K. Gel permeation chromatography (GPC) analyses were measured on a TSKgel G3000PWxl column, where the eluent was 0.1 M citric acid with 0.025 w/w% sodium azide in water, using a flow rate of 0.55 mL/min, and applying an RI (Shimadzu RID-10A) detector. The gadolinium content of the dendrimers was measured with Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES) (Philips Innovation Services, Eindhoven, The Netherlands).

*Synthesis*



*Supplementary Figure S1: Synthesis of G2-PPI-(PEG6-GdDOTA)8 and G5-PPI-(PEG6-GdDOTA)64 (****G2*** *and* ***G5****, respectively). The building block with a discrete number of ethylene glycol units (****1****) was synthesized in 5 steps according to literature procedure (*[*2-4*](#_ENREF_2)*). The molecular structure of the G2-PPI-(NH2)8 starting material is drawn in the box. For convenience, the G2 and G5 PPI core structures are abbreviated with circle cartoons. a) PyBOP, DiPEA, DCM; b) TFA, DCM; c) DOTA-NHS ester, TEA, MeOH; d) Gd(OAc)3, H2O, pH~7.*

The synthesis and characterization of the Gd-based MRI contrast agents **G2** and **G5** is described below, adding more detail to data previously reported ([5](#_ENREF_5)). See also Supplementary Figure S1 for the synthetic route to **G2** and **G5**.

*[2-(2-{2-[2-(2-tert-Butoxycarbonylamino-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]acetic acid (****1****)*

Compound **1** was prepared in 5 steps, mostly as according to literature synthetic and purification procedures. Briefly, hexaethylene glycol was mono-tosylated with tosyl chloride to acquire 2[-2-(2-{2-[2-(2-hydroxyethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethyl p-tosylate ([2](#_ENREF_2)). Next, the tosylate moiety was converted to an azide group by reaction with NaN3 to arrive at compound 2[-2-(2-{2-[2-(2-hydroxyethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethyl azide ([3](#_ENREF_3)). Reduction of the azide using Pd/C and Hto give 2[-2-(2-{2-[2-(2-hydroxyethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]- ethyl amine, was followed by protection of the amine by reaction with di-tert-butyl dicarbonate ([2](#_ENREF_2)). Purification gave tert-butyl 17-hydroxy-3,6,9,12,15-pentaoxaheptadec-1-ylcarbamate: the precursor to **1**. In the final step the hydroxy end group was converted to a carboxylic acid group by adaptation of an oxidation method as described by Araki et al. that employs NaOCl, NaBr and TEMPO ([4](#_ENREF_4)).

Particularly, TEMPO (60 mg, 0.38 mmol) and NaBr (57 mg, 0.55 mmol) were added to a 13% solution of NaOCl (2 mL), saturated NaHCO3 (2 mL) and water (20 mL). The solution was stirred until the TEMPO had dissolved. Subsequently, tert-butyl 17-hydroxy-3,6,9,12,15-pentaoxaheptadec-1-ylcarbamate (0.3 g, 0.79 mmol) was added and the mixture was stirred for 1 hour at room temperature. A saturated solution of NaHSO3 (2 mL) was added, and the crude mixture was extracted with CHCl3 to remove TEMPO and organic by-products. The pH of the water layer was then lowered to pH=1 by addition of an HCl solution, and the water layer was subsequently extracted with CHCl3 (four times). After drying of the collected organic layers over Na2SO4, the solvent was evaporated *in vacuo*, resulting in the colorless oil **1** (0.3g, 0.76 mmol, 96%).

1H NMR (CDCl3):  = 9.1 (br, COO*H*), 5.1 (br, N*H*), 4.12 (s, 2H, O-C*H2*-COOH), 3.75-3.52 (m, 16H, OC*H2*), 3.50 (t, *J* = 5.2 Hz, 2H, OC*H2*), 3.27 (q, *J* = 6.1, 5.5 Hz, 2H, C*H2*NH), 1.40 (s, 9H, C-C*H3*). 13C NMR (CDCl3):  = 172.5 (OH*C*=O), 156.1 (NH*C*=O), 79.0 (*C*-CH3), 71.0 (O*C*H2-CH2-NH), 70.5-70.1 (*C*H2O), 68.7 (O*C*H2COOH), 40.3 (*C*H2NH), 28.4 (C-*C*H3). LC-ESI-MS: Rt = 4.66 min, m/z calcd (C17H33NO9) 395.5; found 418.3 [M+Na]+, 296.3 [M+H-Boc]+ (Supplementary Figure S2).



*Supplementary Figure S2. LC-MS chromatogram of* ***1*** *(left) with the corresponding MS-spectrum (right) of the dominant LC-peak at t = 4.66 min. Apart from the Na+-adduct of the product, also the BOC-deprotected molecule is observed in the MS-spectrum; de-protection takes place during the MS ionization.*

*G2-PPI-(PEG6-NHBoc)8 (****2****)*

G2-PPI-(NH2)8 (102 mg, 132 μmol), **1** (500 mg, 1.3 mmol, 1.2 eq per NH2) and *N*,*N*-diisopropylethylamine (0.66 mL, 3.8 mmol, 3 eq to **1**) were dissolved in dichloromethane (6 mL). After the addition of PyBOP (658 mg, 1.3 mmol, 1.2 eq per NH2) and dichloromethane (1 mL) the solution was stirred at room temperature for 2 h. Chloroform (150 mL) was added and the solution was washed twice with 0.1 M NaOH (40 mL). The organic layer was dried using Na2SO4, filtrated and the solvent was removed *in vacuo*. The residue was stirred in ether and the ether layer was decanted off (2x). Preparative size-exclusion chromatography (Sephadex G25, H2O) yielded **2** (500 mg, 132 μmol, 100%) as a yellowish oil. 1H-NMR (CD3OD): *δ* = 3.91 (s, 16H, COC*H*2), 3.65-3.52 (m, 144H, C*H*2O), 3.43 (t, 16H, C*H*2O), 3.19-3.16 (br, 16H, N*H*), 3.14 (q, 16H, C*H*2NH), 2.55-2.40 (m, 36H, C*H*2NC*H*2), 1.62-1.46 (m, 28H, NCH2C*H*2CH2N, NCH2C*H*2C*H*2CH2N), 1.35 (s, 72H, C(C*H*3)3). 13C-NMR(CD3OD): *δ* = 172.55, 158.42, 80.21, 71.88, 71.48, 71.43, 71.33, 71.28, 71.20, 71.04, 52.98, 52.48, 47.31, 41.23, 38.48, 28.85, 28.78, 27.50. ESI-MS m/z calcd (C176H344N22O64) 3792.8 g/mol; found 948.9 [M+4H]4+, 1265.1 [M+3H]3+ and 1896.8 [M+2H]2+. FT-IR (ATR): *υ* (cm-1) = 3346, 2869, 1707, 1664, 1530, 1455, 1391, 1365, 1275, 1250, 1104, 1043, 947, 863, 845, 781, 758, 578.

*G2-PPI-(PEG6-NH2)8 (****4****)*

Under an Ar atmosphere, **2** (500 mg, 132 μmol) was dissolved in dichloromethane (5 mL). The flask was put on an ice bath, TFA (5 mL) was added and the solution was stirred at room temperature for 2 h. The solvent was removed *in vacuo*, followed by co-evaporation with toluene (2x). The oil was then washed with ether to further remove TFA. Amine **4** (430 mg) was obtained as a yellowish oil that still contained residual TFA. 1H-NMR (CD3OD): *δ* = 4.04 (s, 16H, COC*H*2), 3.73-3.63 (m, 144H, C*H*2O), 3.34-3.24 (m, 52H, C*H*2NH, C*H*2NC*H*2), 3.13 (t, 16H, C*H*2NH3+), 2.28 (br, 8H, NCH2C*H*2CH2N), 1.98 (m, 16H, NCH2C*H*2CH2N), 1.85 (br, 4H, NCH2C*H*2C*H*2CH2N). 13C-NMR (CD3OD): *δ* = 171.8, 161.0 (q, TFA), 116.6 (q, TFA), 70.4, 70.0, 69.9, 69.7, 66.5, 50.5, 49.3, 39.2, 35.6, 23.6. ESI-MS m/z calcd (C136H280N22O48) 2991.8 g/mol; found 499.8 [M+6H]6+, 599.6 [M+5H]5+, 749.0 [M+4H]4+, 998.3 [M+3H]3+ and 1496.6 [M+2H]2+. FT-IR (ATR): *υ* (cm-1) = 3421, 2881, 1673, 1537, 1472, 1424, 1350, 1290, 1250, 1200, 1178, 1123, 948, 832, 800, 721, 597, 519.

*G2-PPI-(PEG6-DOTA)8 (****6****)*

Amine **4** (395 mg, 132 μmol) was dissolved in methanol (5 mL) and triethylamine (2.2 mL, 15.8 mmol, 120 eq). Thereafter, *N*-hydroxysuccinimide activated DOTA (DOTA-NHS ester; 1.32 g, 2.64 mmol, 1.5 eq per NH2) was added. Note that triethylamine is used in excess to neutralize the residual TFA in amine **4**, and further note that NHS-activated DOTA also contains residual TFA and has an estimated purity of 62%. The solution was stirred at r.t. for 24 h, and was concentrated *in vacuo*. Preparative size-exclusion chromatography (Sephadex G-25, H2O) yielded **6** (700 mg, 0.115 mmol, 87%) as a tough oil. 1H-NMR (D2O): *δ* = 4.11 (s, 16H, COC*H*2), 3.86-3.02 (m, 404H, C*H*2O, COC*H*2N, NC*H*2C*H*2N, C*H*2NH, C*H*2NC*H*2), 2.18 (br, 8H, NCH2C*H*2CH2N), 1.98 (m, 16H, NCH2C*H*2CH2N), 1.77 (br, 4H, NCH2C*H*2C*H*2CH2N). ESI-MS m/z calcd (C136H280N22O48) 6083.1 g/mol; found 761.6 [M+8H]8+, 870.1 [M+7H]7+, 1014.9 [M+6H]6+, 1217.7 [M+5H]5+ and 1521.5 [M+4H]4+. FT-IR (ATR): *υ* (cm-1) = 3418, 2870, 1704, 1622, 1464, 1435, 1387, 1322, 1245, 1104, 1088, 1006, 936, 840, 716, 570, 499.

*G2-PPI-(PEG6-GdDOTA)8 (****G2****)*

Dendrimer ligand **6** (700 mg, 0.115 mmol) was dissolved in H2O (10 mL) and the pH was adjusted to 7.0 using 1 M NaOH. Gd(OAc)3∙xH2O (764 mg, 1.84 mmol, 2 eq per DOTA) in H2O (4 mL, dissolved by shortly heating) was added, and the pH was again adjusted to 7.0 using 1 M NaOH. The solution was stirred at r.t. for 4 days, thereafter it was concentrated *in vacuo.* Preparative size-exclusion chromatography (Sephadex G-25, H2O) and a PD10 column (H2O) yielded **G2** (600 mg, 82 μmol, 71%) as an off-white solid after lyophilization. A xylenol orange test was negative, so the material did not contain free gadolinium ions. The material gave a clear colorless solution in phosphate buffered saline (PBS). ESI-MS m/z calcd (C264H464Gd8N54O104) 7316.9 g/mol; found 915.6 [M+8H]8+, 1046 [M+7H]7+, 1220.7 [M+6H]6+, and 1464.3 [M+5H]5+ (Supplementary Figure S3). FT-IR (ATR): υ (cm-1) = 3372, 3264, 2869, 1595, 1463, 1434, 1387, 1317, 1283, 1243, 1084, 1103, 937, 905, 839, 801, 716, 644, 566, 496. Aqueous GPC showed a dominant peak with a shoulder at lower retention time (so at higher molecular weight), as also observed for related PEGylated PPI-based materials ([6](#_ENREF_6)) (Supplementary Figure S3). ICP-MS Gd: calcd wt%= 17.2%, found wt% = 14.8%.

A similar procedure as described above for the **G2** dendrimer was followed for the synthesis of the **G5** product.

*G5-PPI-(PEG6-NHBoc)64 (****3****)*

Yield: 355 mg (100%) as a yellowish oil. 1H-NMR (CD3OD): *δ* = 7.32 (t, 64H, N*H*COCH2), 5.22 (br, 64H, N*H*COO), 3.96 (s, 128H, COC*H*2), 3.72-3.56 (m, 1152H, C*H*2O), 3.52 (t, 128H, C*H*2O), 3.28 (q, 128H, C*H*2NH), 2.42 (m, 372H, C*H*2NC*H*2), 1.70-1.50 (m, 252H, NCH2C*H*2CH2N, NCH2C*H*2C*H*2CH2N) , 1.43 (s, 576H, C(C*H*3)3). 13C-NMR (CD3OD): *δ* = 169.8, 156.0, 78.9, 70.7, 70.5, 70.4, 70.2, 70.14, 70.08, 52.3, 51.8, 51.4, 40.2, 37.3, 28.4, 26.9, 23.9. FT-IR (ATR): *υ* (cm-1) = 3346, 2931, 2869, 2817, 1707, 1660, 1530, 1455, 1391, 1365, 1349, 1273, 1249, 1170, 1099, 1042, 947, 862, 845, 780, 757, 732, 698.

*G5-PPI-(PEG6-NH2)64 (****5****)*

During work-up, part of the TFA was removed by co-evaporating the oil with toluene. The oil was then dissolved in MeOH and precipitated in ether to further remove TFA. Yield: 360 mg (contains residual TFA). 1H-NMR (CD3OD): *δ* = 4.00 (s, 128H, COC*H*2), 3.72-3.56 (m, 1152H, C*H*2O), 3.36-3.16 (m, 500H, C*H*2NH, C*H*2NC*H*2), 3.15 (t, 128H, C*H*2NH3+), 2.28 (br, 120H, NCH2C*H*2CH2N), 1.95 (m, 128H, NCH2C*H*2CH2N), the signal of the NCH2C*H*2C*H*2CH2N group is not differentiated. 13C-NMR (CD3OD): *δ* = 171.6, 161.0 (q, TFA), 116.6 (q, TFA), 70.4, 70.0, 69.9, 69.7, 66.5, 50.5, 49.5, 39.2, 35.6, 23.6, 18.2. FT-IR (ATR): *υ* (cm-1) = 3334, 3092, 2880, 1668, 1541, 1471, 1455, 1422, 1350, 1293, 1251, 1198, 1177, 1118, 947, 832, 799, 720, 707, 595, 558, 518.

*G5-PPI-(PEG6-DOTA)64 (****7****)*

Preparative size-exclusion chromatography (Sephadex G-25, H2O) yielded **7**(420 mg, 60%) as a tough oil. 1H-NMR (D2O): *δ* = 4.10 (s, 128H, COC*H*2), 3.88-3.00 (m, 3320H, C*H*2O, COC*H*2N, NC*H*2C*H*2N, C*H*2NH, C*H*2NC*H*2), 1.97 (br, 252H, NCH2C*H*2CH2N, NCH2C*H*2C*H*2CH2N). FT-IR (ATR): *υ* (cm-1) = 3346, 2917, 2876, 1708, 1664, 1530, 1455, 1391, 1365, 1275, 1254, 1104, 1043, 947, 863, 845, 781, 578.

*G5-PPI-(PEG6-GdDOTA)64 (****G5****)*

Preparative size-exclusion chromatography (Sephadex G-25, H2O) and a PD10 column (H2O) yielded **G5** (420 mg, 83%) as an off-white solid after lyophilization. A xylenol orange test was negative, so the material did not contain free gadolinium ions.

FT-IR (ATR): *υ* (cm-1) = 3376, 2917, 2869, 1591, 1457, 1435, 1393, 1369, 1319, 1245, 1084, 1003, 393, 840, 801, 716, 558, 495. Aqueous GPC showed a dominant peak with a minor shoulder at lower retention time (so at higher molecular weight), as also observed for related PEGylated PPI-based materials ([6](#_ENREF_6)) (Supplementary Figure S3). ICP-MS Gd: calcd wt%= 16.9%, found wt% = 14.3%.



*Supplementary Figure S3. Left: ESI-MS spectrum of G2-PPI-(PEG6-GdDOTA)8 (****G2****). The dominant peaks all correspond to the molecular structure of* ***G2****. Right: GPC-traces of* ***G2*** *and* ***G5*** *showing a distinctly lower retention time, and thus elution volume, for the* ***G5*** *material indicating its higher hydrodynamic volume.*

*Dynamic Light Scattering (DLS)*

The hydrodynamic size of the G2-PPI-(PEG6-GdDOTA)8 (**G2**) and G5-PPI-(PEG6-GdDOTA)64 (**G5**) dendrimers was determined with DLS on a Zetasizer Nano-S (Malvern Instruments, Malvern, Worcestershire, United Kingdom) at 20°C using the volume-weighted particle size distribution. The dendrimers were dissolved in filtered PBS of pH 7.4 and the obtained solutions were filtered through a 0.45 µm pore Millex membrane filter (Merck Millipore Ltd., Tullagreen, Carrigtwohill, County Cork, Ireland) to remove dust or other potential contaminants that may affect the DLS measurements. The results of the DLS measurements are shown in Supplementary Figure S4. The volume-weighted size distribution showed a single peak for the **G2** and **G5** dendrimers and a narrow size distribution. The average hydrodynamic diameter and distribution widths of the **G2** and **G5** dendrimers were 4.4±1.2 and 10.0±4.5 nm, respectively.

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*Supplementary Figure S4: The volume-weighted size (hydrodynamic diameter) distribution of the* ***G2*** *and* ***G5*** *dendrimer measured in PBS of pH 7.4 at 20°C.*

*Relaxivity in mouse serum*

The longitudinal (r1) and transverse (r2) relaxivities were determined by measuring the relaxation rates of 6 tubes containing ~0.02-1.0 mM gadolinium in Balb/c mouse serum (Innovative Research, Novi, MI, United States) at 7 T at 37°C (Supplementary Table S1). All measurements were performed on a 7 T Bruker BioSpec 70/30 USR (Bruker BioSpin MRI GmbH, Ettlingen, Germany) equipped with a 1H 112/072 (outer/inner diameter) circular polarized MRI transceiver volume coil (Bruker BioSpin MRI GmbH, Ettlingen, Germany). R1 relaxation rates were measured using an inversion recovery sequence and R2 relaxation rates were measured using a multi spin-echo sequence.

*Supplementary Table S1: Longitudinal (r1) and transverse (r2) relaxivities measured in Balb/c serum at 7 T at 37°C .*

|  |  |  |  |
| --- | --- | --- | --- |
| **Contrast agent** | **r1 (mM-1\*s-1)** | **r2 (mM-1\*s-1)** | **r2/r1 (-)** |
| Gadoterate meglumine | 3.1 | 3.5 | 1.2 |
| G2-PPI-(PEG6-GdDOTA)8 | 5.2 | 6.2 | 1.2 |
| G5-PPI-(PEG6-GdDOTA)64 | 5.9 | 8.1 | 1.4 |

**Supplementary Information 2: Histopathological analysis of tumor perfusion**

The skin was removed from the tumors and four lines of different colors were drawn on the tumor using a tissue-marking dye kit (Sigma-Aldrich). These lines facilitated retrieval of the orientation of excised tumors, such that that the orientation of tissue sections could be matched with the MRI slice orientation. After excision, the tumor was placed in a dedicated tissue holder and cut into two pieces, such that the cutting face matched with the orientation of the central MRI slice (using the color lines and the anatomical MRI images as a reference). Both pieces were subsequently embedded in Cryomatrix (Shandon, Thermo Scientific, Waltham, MA, USA), snap-frozen in isopentane (Sigma-Aldrich) at -160°C and stored at -80°C until further processing.

In correspondence with the MRI slice thickness, every 1500 μm, frozen tumor sections (5 μm) were cut and mounted on poly-L-lysine–coated slides (Menzel, Braunschweig, Germany). The sections were fixed in cold acetone (4°C) for 10 minutes. Subsequently, slides were scanned for the Hoechst signal before staining of the vessel marker. After scanning of the Hoechst signal and between all consecutive steps of the staining process, sections were rinsed 3 times for 5 minutes in 0.1 M phosphate-buffered saline, pH 7.4 (Klinipath, Duiven the Netherlands). To stain the blood vessels, sections were incubated with undiluted 9F1 supernatant (rat monoclonal antibody against mouse endothelium (generously supplied by the Department of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands) for 45 minutes at 37°C, followed by incubation with chicken anti-rat-Alexa647 (Molecular Probes, Leiden, The Netherlands), 1:100 in PAD (primary antibody diluent, (AbD Serotec, Kidlington, UK*)* for 45 minutes at 37°C. Finally, sections were mounted in Fluoromount (Serva, Heidelberg, Germany).

Tumor sections were analyzed by a semi-automated microscope scanning system as described previously ([7](#_ENREF_7)). Briefly, sections were scanned (100x magnification, resolution 2.535 μm/pixel) for Hoechst and 9F1 using a digital image processing system, consisting of a high-resolution 14 bit camera (Coolsnap HQ2, Hamamatsu Photonics, Almere, The Netherlands) on a fluorescence microscope (Axio Scope A1, Zeiss, Göttingen, Germany) and computer-controlled motorized stepping stage (MAC 6000, Ludl Electronics Products LTD, Hawthorne, NY, USA). Image processing was done using IVision software (Scanalytics Inc, Fairfax, VA, USA) on a Macintosh (Cupertino, CA, USA) computer. The obtained gray-scale images were converted to binary images for further analysis using ImageJ software (NIH, Bethesda, MD, USA). Thresholds for the fluorescent signals were interactively set above the background. The tumor area of each section was delineated guided by consecutive H&E stained tumor sections (i.e. excluding skin/muscle tissue). The perfused vessel fraction (PF) of the tumor was calculated as the number of pixels of the perfused vascular area divided by the number of pixels of the vascular area. The vascular density (VD) was calculated as the number of vascular structures per mm2 ([8](#_ENREF_8)).

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