ADVANCED HEALTHCARE MATERIALS

Supporting Information

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Protease responsive nanogels for transcytosis across the blood brain barrier and intracellular delivery of radiopharmaceuticals to brain tumor cells

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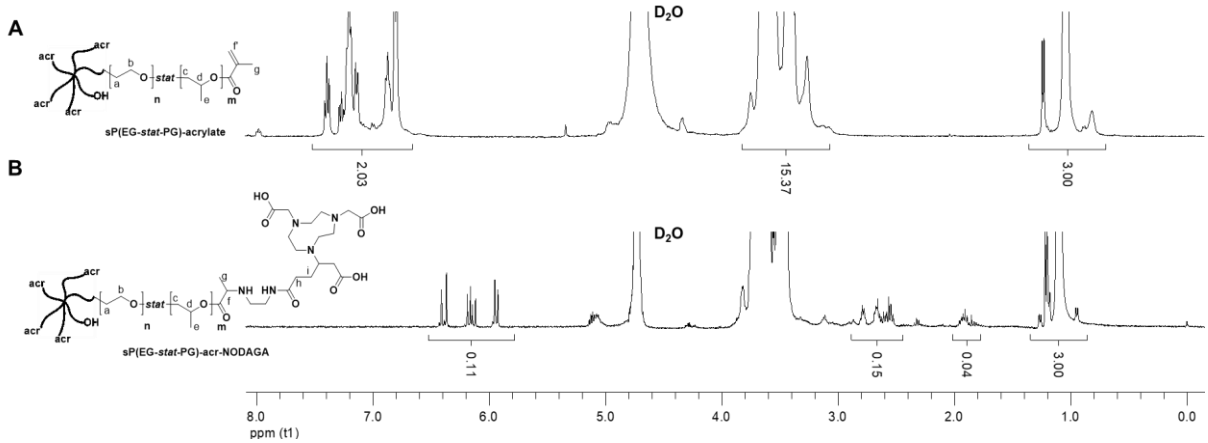

Figure S1. ^{1}H°NMR (400 MHz) of sP(EG-stat-PG)-acr-NODAGA in D_2O. (A) sP(EG-*stat*-PG)-acrylate. (B) sP(EG-stat-PG)-acr-NODAGA after successful covalent linking of the chelator (NODAGA) to the pre-polymer structure.

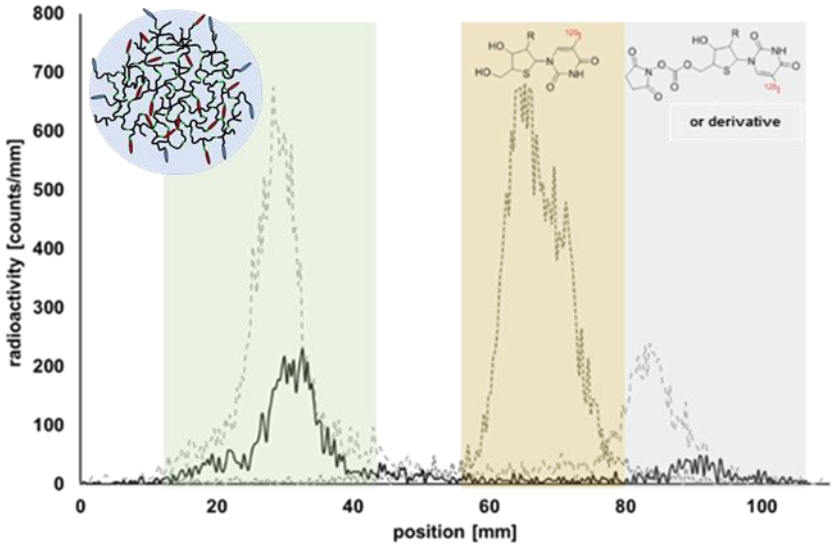

Figure S2. Quality control of ITdU-NG. Excess of low molecular weight byproducts was removed via PD-10 desalting column; Thin layer chromatograph of [^{125}I]ITdU-nanogels

before purification (dashed line) and after purification (PD-10) (black line) and of sole [^{125}I]ITdU (stationary phase: TLC Silica gel 60, mobile phase: ethanol: H_2O: acetonitrile (8:1:1)).

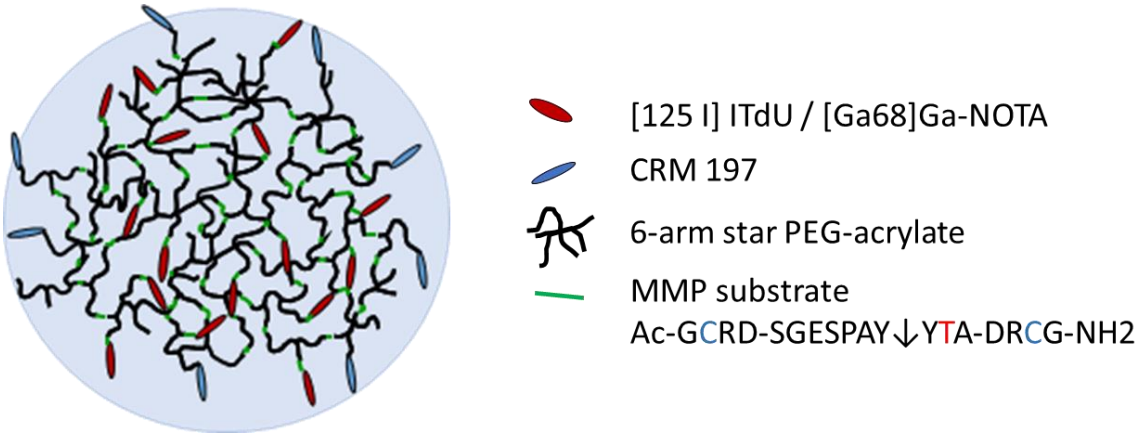

Figure S3. Illustration of nanogels modified with CRM-197 and cross-linked with MMP-substrate (blue cysteine; red tyrosine) for cross-linking and functionalization for radioactive labeling.

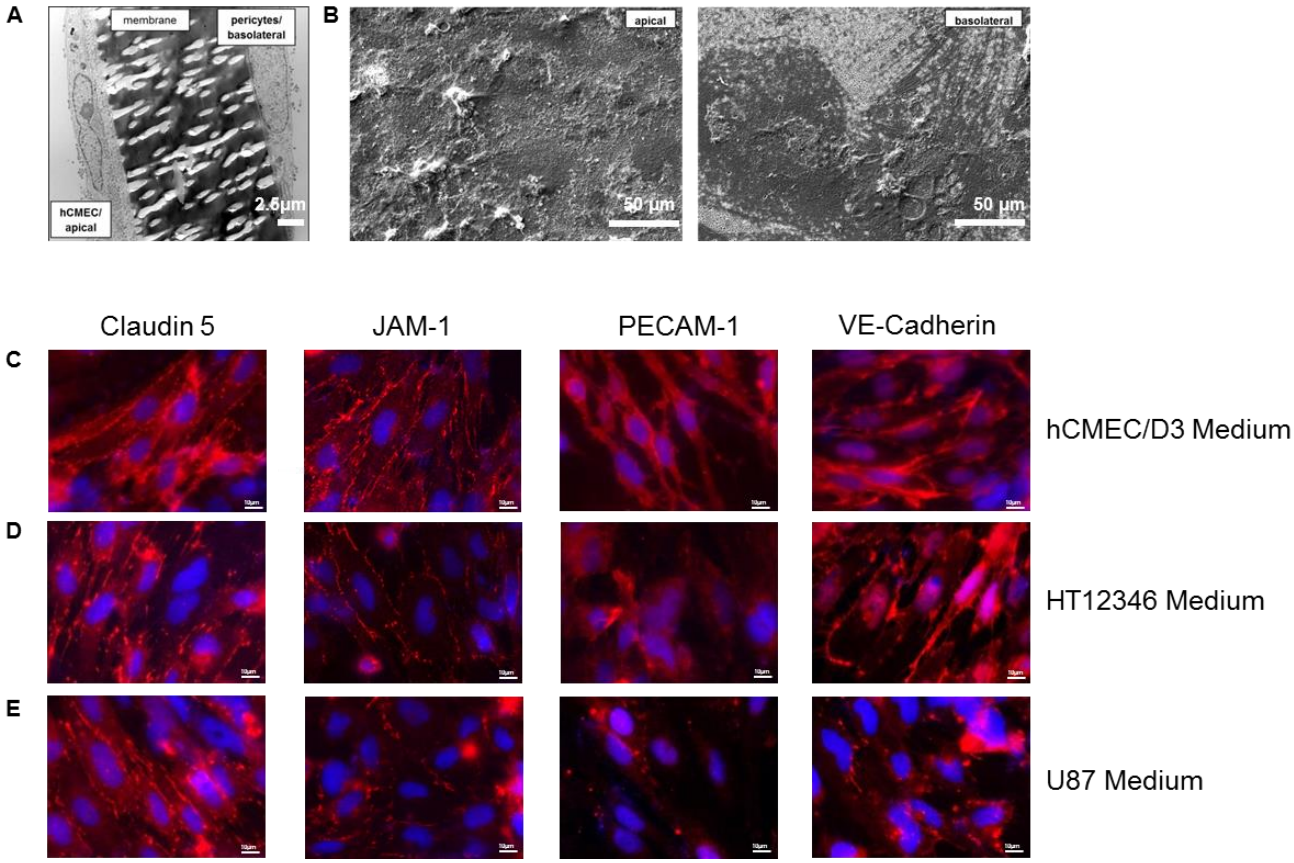

Figure S4. The integrity of the blood brain barrier *in vitro* model. (A) TEM image of an intact BBB with hCMEC cells seeded on a collagen matrix onto the membrane of the insert and pericytes on the basolateral side of the insert; REM images of (B) apical (hCMEC/D3) and basolateral (pericytes) side of the membrane. (C-E) Expression of tight junction proteins in hCMEC cells in (C) mono-culture, (D) co-culture with HT 12346 and (E) co-culture with U-87 cells (3 days).

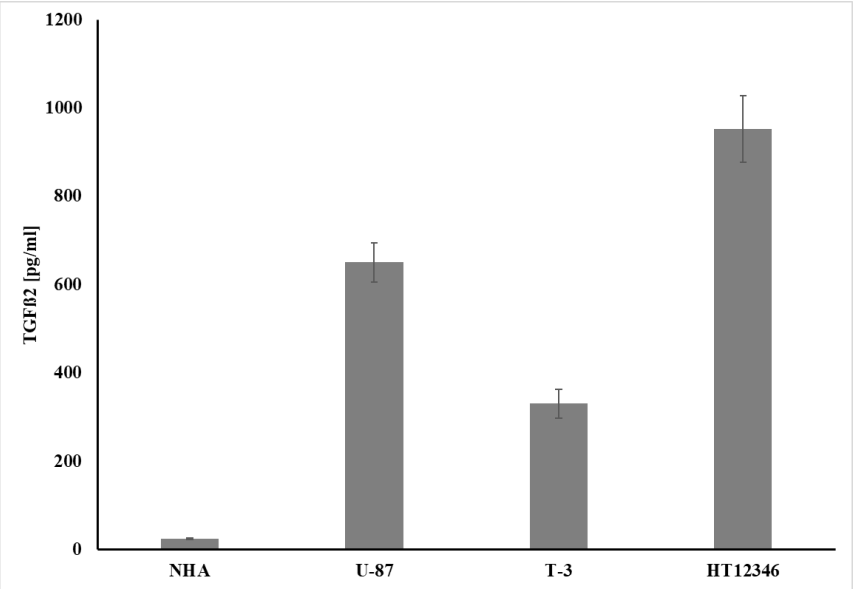

Figure S5. TGFß2 secretion by NHA and glioblastoma cells was quantified using ELISA. TGFß2 concentration was evaluated in the cell culture supernatants and calculated as pg/ml medium (n = 5).

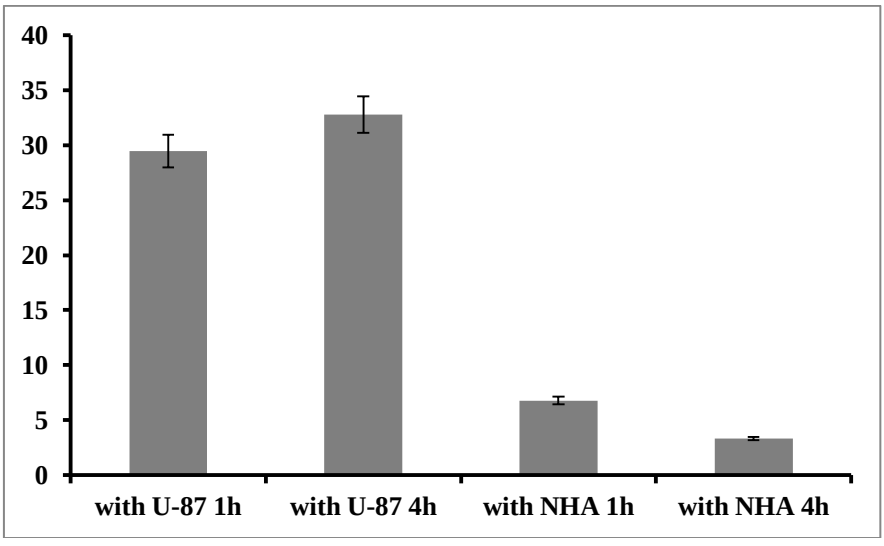

Figure S6. Drug release from [^{125}I]ITdU-CRM-197-nanogel in cell culture media of U-87 and NHA after 1 h and 4 h incubation time (n = 5).