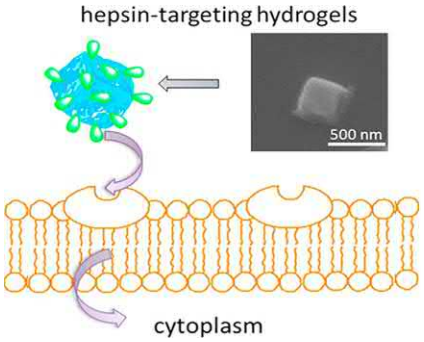

FIG. 3 Schematic illustration of hepsin-targeting hydrogels and cellular uptake. (Reprinted from B. Xue, et al., Peptide-functionalized hydrogel cubes for active tumor cell targeting, Biomacromolecules 19 (10) (2018) 4084–4097 with permission from American Chemical Society.)

attention in the delivery of drugs to the brain because of their unique features such as cheapness and low immunogenicity. Glutathione (GSH) is a shuttle peptide that crosses the BBB has reached clinical application stages [42]. In this regard, Nosrati et al. developed an efficient system for the delivery of paclitaxel (PTX) from the BBB by synthesis of magnetic nanoparticles and the conjugation of GSH on the surface of synthesized nanoparticles, and also monitored the delivery by MRI [43]. Also in a series of studies, GSH-PEGylated liposomes were developed and studied to increase the delivery efficiency of the opioid peptide DAMGO (H-Tyr-d-Ala-Gly-MePhe-Gly-ol) [44]. Another work showed that encapsulation of DAMGO peptide in PEGylated liposomes with or without GSH leads to increased brain uptake of this peptide [45]. In addition, specific uptake of GSH-conjugated PEGylated liposomes by the receptor revealed the ability of GSH in brain targeting [46].

PEG-modified polyamidoamine dendrimer (PAMAM) conjugated to the HAIYPRH peptide (T7) and loaded with doxorubicin targeted transferrin receptors which are highly expressed on tumor cells. It was found that the presence of T7 ligand increased the cellular uptake of nanoformulation mediated by transferrin receptor and also increased the accumulation of doxorubicin in the tumor site compared to the T7-free nanocomplex. The T7-conjugated nanocomplex also showed more tumor growth inhibition than the T7-free nanocomplex, indicating that the T7 peptide could be used as an effective ligand in active targeting (Fig. 4) [47].

2.3. Folic Acid

FA (vitamin B) is a water-soluble vitamin with a molecular weight of 441 Da. This biomolecule is essential for the synthesis, methylation and repair of DNA molecules. FA is stable at various pH and temperatures and also retains its ability to binding to its receptor on the cell, when bound to other molecules and drugs [48]. The FA receptor, because of its high expression on cancer cells, can be used to specifically target in cancer treatment. Actually, the FA receptor on cancer cells is an important biomarker known for cancer cells. This receptor enables the detection of cancer cells through specific imaging and the treatment of cancer cells (targeted drug delivery). Actually, by binding FA to a formulation, it can be targeted specifically to cancer cells that have a

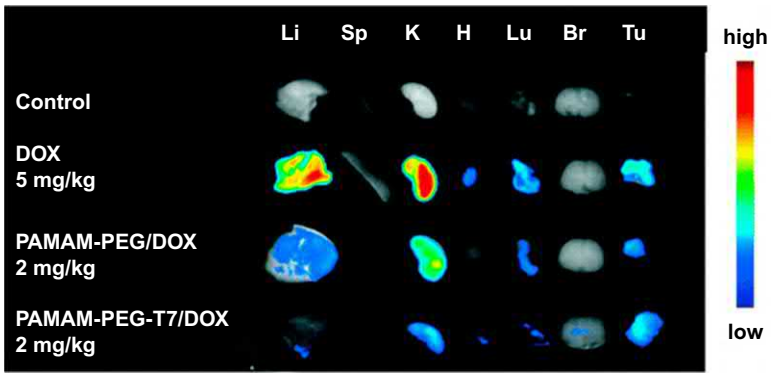

FIG. 4 The biodistribution of DOX in tumor-bearing mice after injection of saline as a control, free DOX, PAMAM-PEG/DOX, and PAMAM-PEG-T7/DOX. *Br*, brain; *H*, heart; *Li*, liver; *Lu*, lung; *K*, kidney; *Sp*, spleen; *Tu*, tumor. (Reprinted from L. Han, et al., Peptide-conjugated PAMAM for targeted doxorubicin delivery to transferrin receptor overexpressed tumors, Mol. Pharm. 7 (6) (2010) 2156–2165 with permission from American Chemical Society.)