

腫瘍内投与製剤

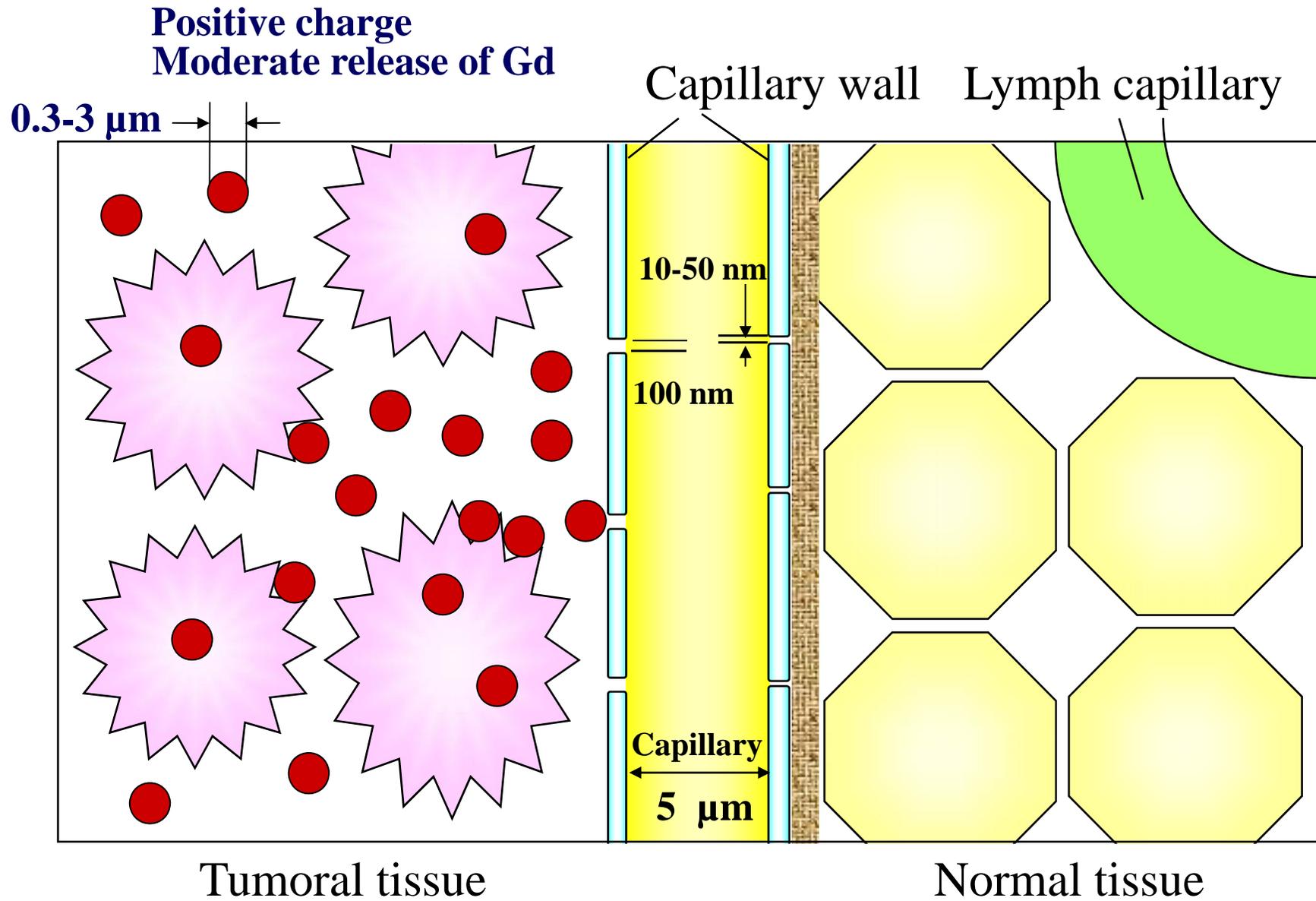
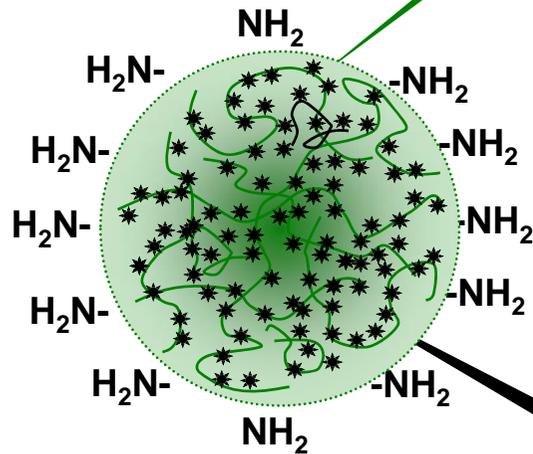
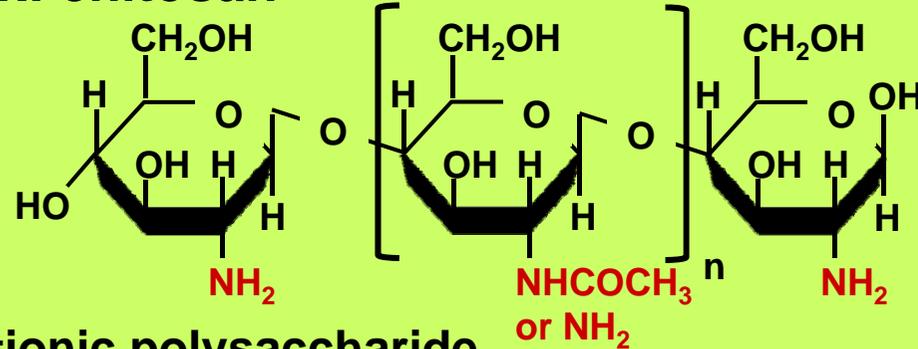


Fig. Properties of Particles to be i. t. Injected

Gadolinium-loaded Chitosan Nanoparticles (Gd-nanoCP)

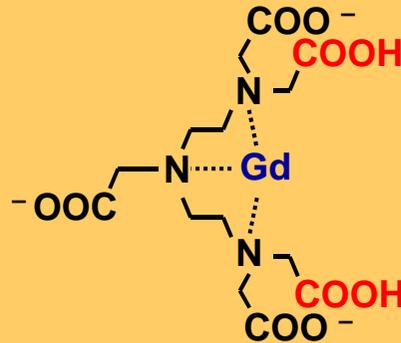


Matrix: chitosan



- Cationic polysaccharide
- Biocompatible, biodegradable, bioadhesive

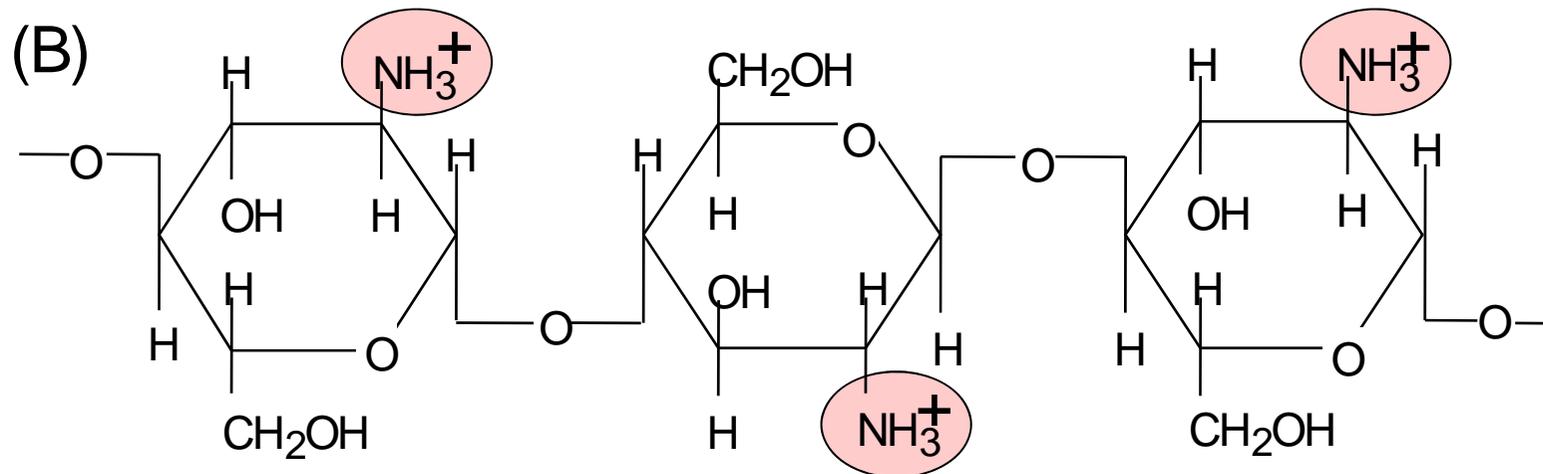
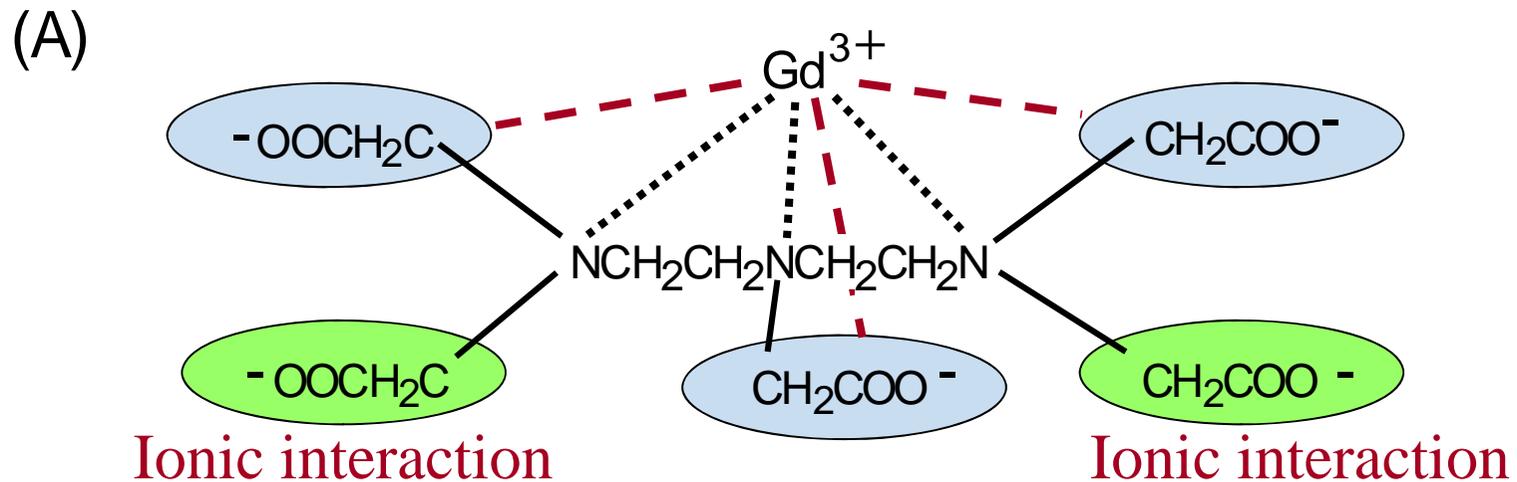
Gd source: gadopentetic acid (Gd-DTPA)



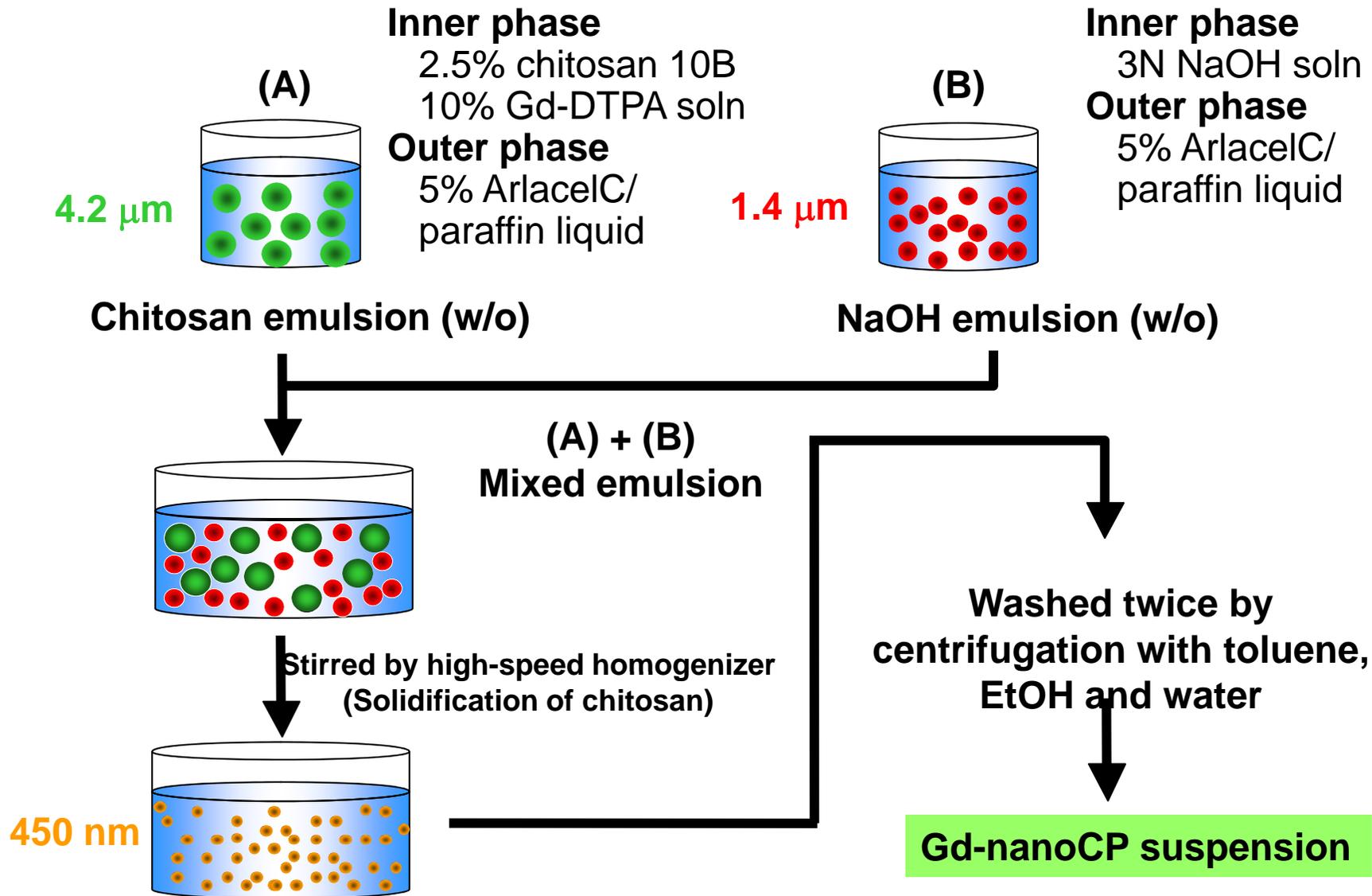
- Main component of Magnevist[®] (MRI contrast agent)
- Highly water-soluble

Gadolinium carrier - Gd-nanoCP

Highly Gd-containing nanoparticles were prepared using cationic polysaccharide, chitosan



Structure of Gadopentetate (Gd-DTPA) (A) and Chitosan (B)



Preparation Process of Gd-nanoCPs Using an Emulsion-Droplet Coalescence Technique

H. Tokumitsu, H. Ichikawa, Y. Fukumori, *Pharm. Res.*, 16, 1830 (1999).

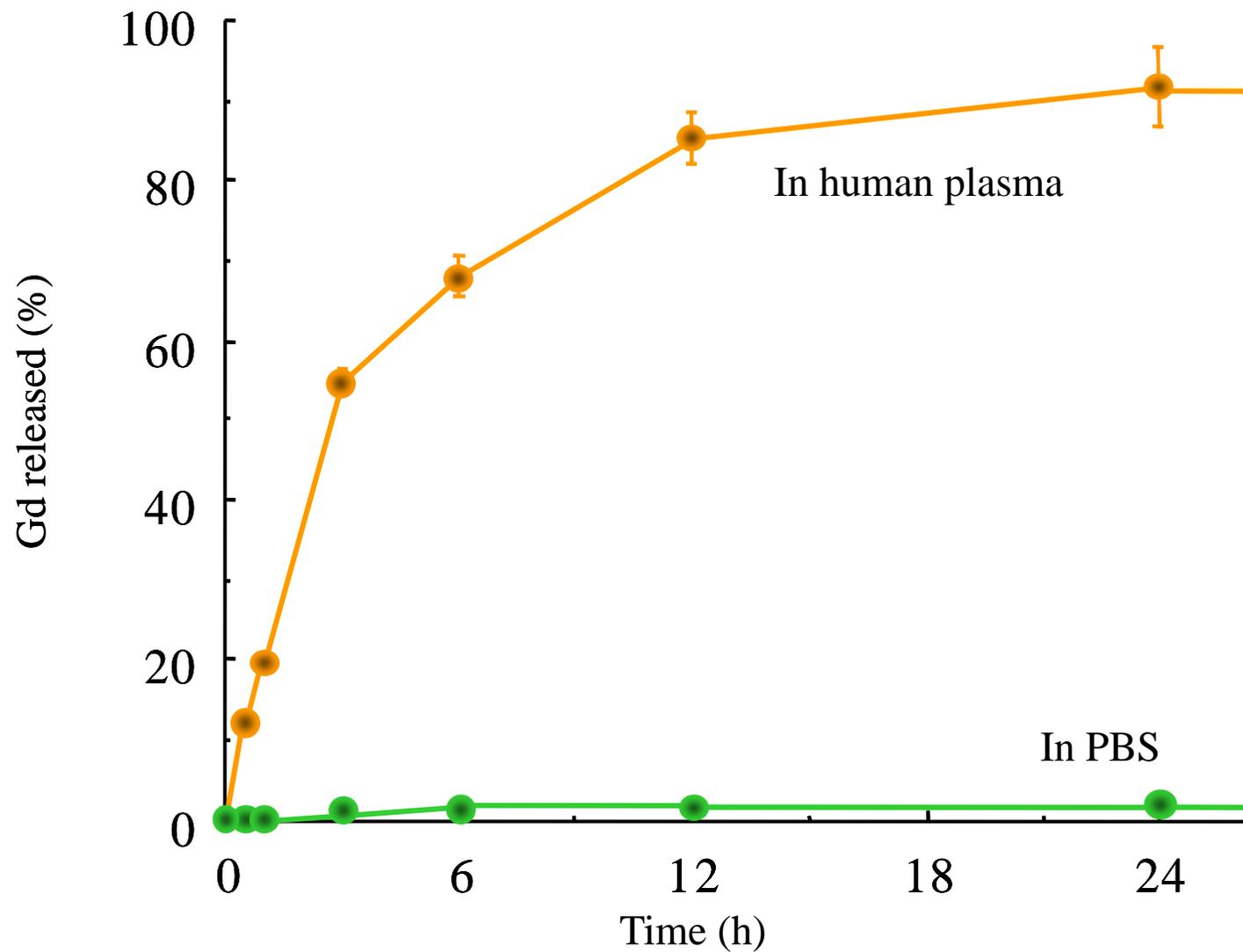
- The Gd content of Gd-nanoCPs prepared by this method using 100% deacetylated chitosan were very high; $9.3 \pm 3.2\%$, equivalent to $32.4 \pm 11.0\%$ as gadopentetic acid (Gd-DTPA). But, the mean particle diameter was 426 ± 28 nm (mean \pm S.D.), which was too large to deliver Gd to tumor by the EPR effect.

Table. Mean Particle Size and Gd Content of Gd-nanoCP Prepared with Various Deacetylated Degrees of Chitosan and Gd-DTPA Concentrations in Chitosan Media

	No. of batch	Mean particle size (nm)*	Gd content (% w/w)* [Gd-DTPA content, %]
Chitosan 10B			
— 5% Gd-DTPA soln	3	461 ± 15	7.7 ± 1.7 [26.9 ± 5.9]
— 10% Gd-DTPA soln	6	426 ± 28	9.3 ± 3.2 [32.4 ± 11.0]
— 15% Gd-DTPA soln	3	452 ± 25	13.0 ± 1.8 [45.3 ± 6.2]
Chitosan 9B			
— 10% Gd-DTPA soln	3	594 ± 96	4.1 ± 1.0 [14.2 ± 3.4]
Chitosan 8B			
— 10% Gd-DTPA soln	3	750 ± 77	3.3 ± 0.8 [11.6 ± 2.7]

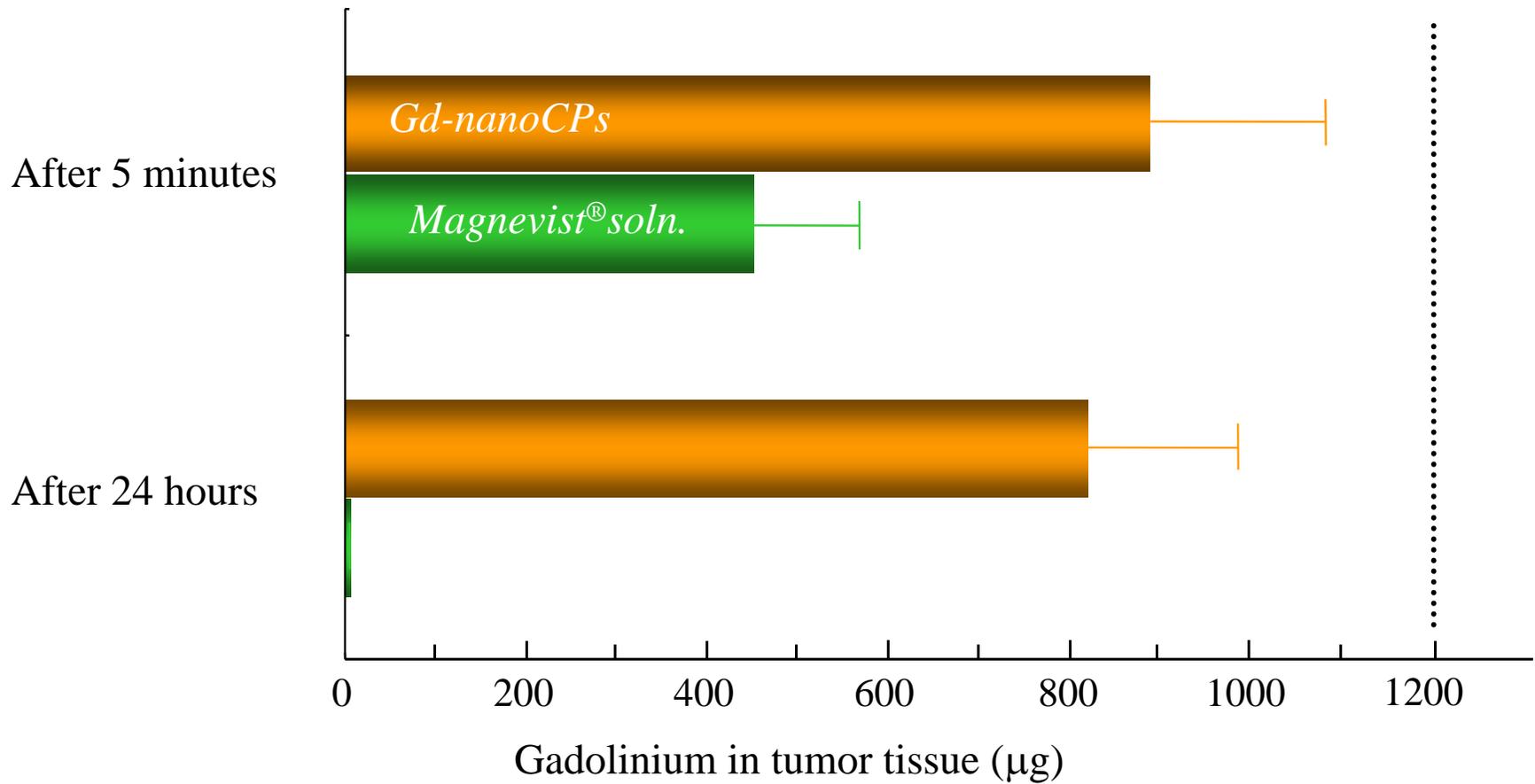
* The value shows average \pm S.D. of 3-6 batches.

H. Tokumitsu, H. Ichikawa, Y. Fukumori, *Pharm. Res.*, 16, 1830 (1999).



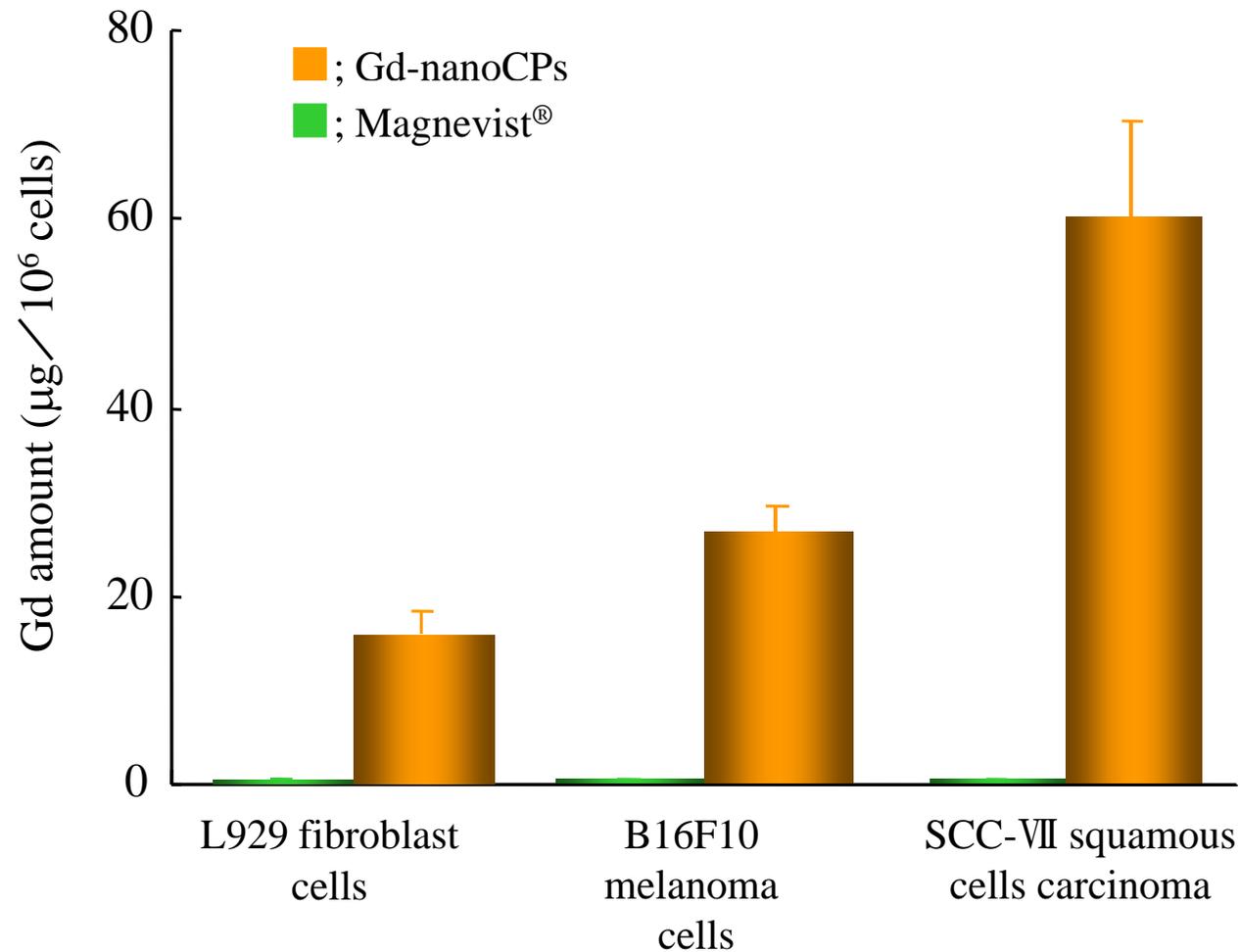
Release of Gd from Gd-nanoCPs in Phosphate Buffered Saline Solution and Human Plasma in Vitro

H. Tokumitsu, H. Ichikawa, Y. Fukumori, *Pharm. Res.*, 16, 1830 (1999).



Amount of Gadolinium in B16F10 Melanoma Tissue on C57BL/6 Mice after Intratumoral Injection of Gd-nanoCP Suspension or Diluted Magnevist® Solution at a Gd Dose of 1200 mg

H. Tokumitsu, H. Ichikawa, Y. Fukumori et al., *Cancer Lett.*, 150, 177 (2000).



Uptake and Adhesion of Gd-nanoCPs (■) or Magnevist® (■) at Gd-Dose of 40 ppm in Three Different Cell Lines 12 hr after Exposure to the Cells under 5% CO₂ Atmosphere at 37°C

F. Shikata, H. Ichikawa, Y. Fukumori et al., *Eur. J. Pharm. Biopharm.*, 53, 57 (2002).

- Gd-containing chitosan nanoparticles (Gd-nanoCPs) injected **via i.t. route** exhibited much stronger tumor-killing effects, clearly depending on dose.
- However, we can not achieve any complete treatments of cancer after administration, possibly coming from inhomogeneous distribution of Gd in the tumor tissue.

SCC-VII squamous cells carcinoma

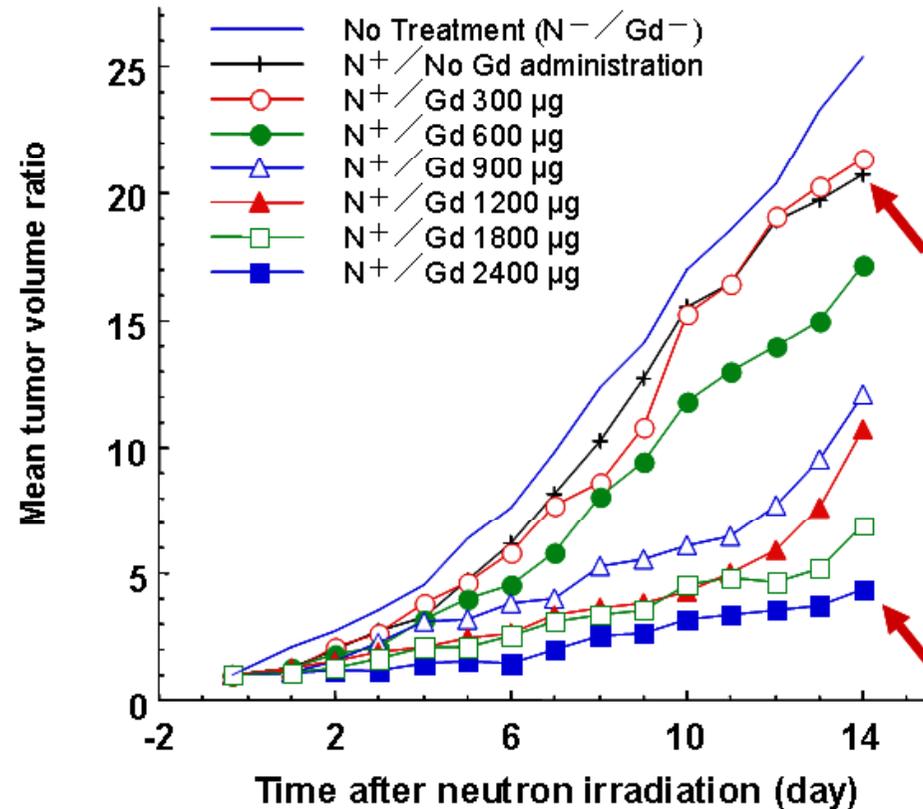


Fig. Effects of Gd Dose on Tumor Growth Inhibition in Gd-NCT Trial by Intratumoral Injection of Gd-nanoCPs

H. Tokumitsu, J. Hiratsuka, Y. Sakurai, F. Shikata, H. Ichikawa, Y. Fukumori, T. Kobayashi.
 Kyoto University Research Reactor Progress Report 1998, Section I, 1999, p.179.