pH-sensitive size-shrinking nanoparticles for cancer therapy

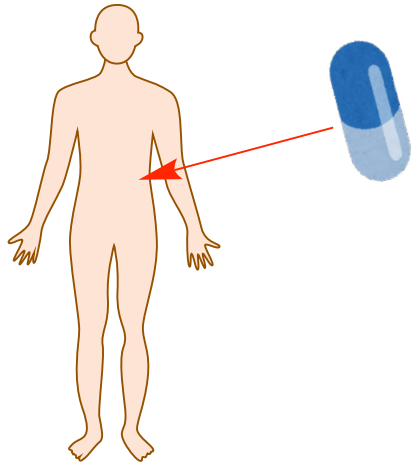
Literature seminar #1

B4 Shinpei Takamaru

2023/01/19 (Thu)

Contents

Drug Delivery Systems



➢What are Drug Delivery Systems?

the method or process of deliver drugs

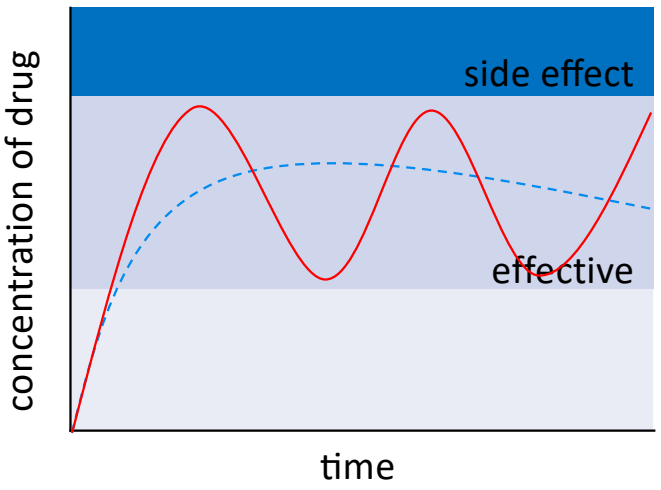
- at the targeted site
- in the desired dose
- at the appropriate time and speed

to achieve therapeutic effects

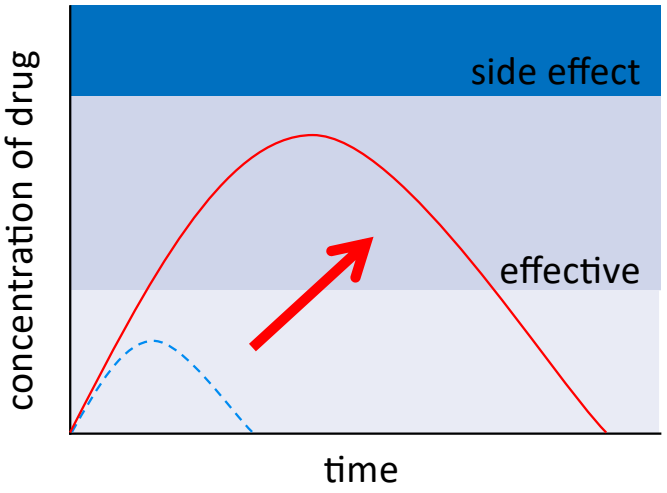
by improving pharmacokinetics and pharmacodynamics of drugs

Tiwari, G., et al. *INTERNATIONAL JOURNAL OF PHARMACEUTICAL INVESTIGATION* **2012**, *2*(1), 2-11.
Retrieved from https://www.sigmaaldrich.com/JP/en/applications/materials-science-and-engineering/drug-delivery

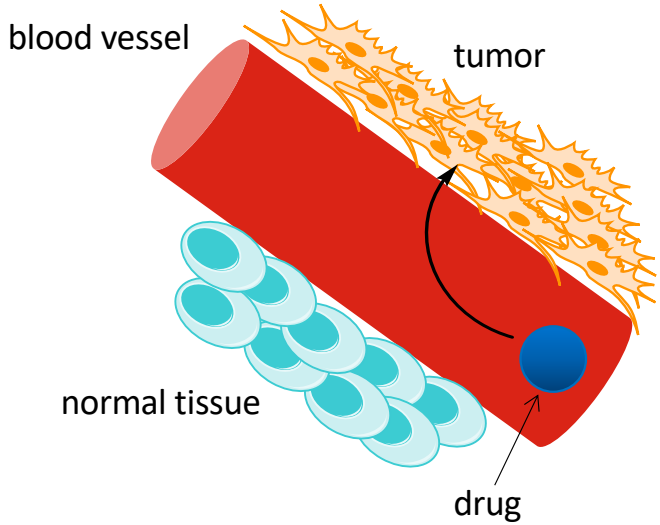
General objectives of DDS



absorption enhancement



controlled release



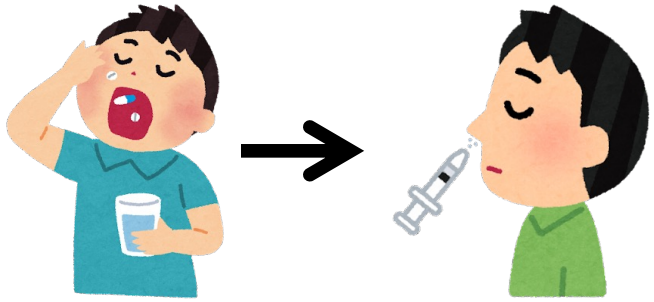
targeting

Okamoto, K. *Yakugaku DDS -DDS seizai to sono yakubutsu chiryou-* [薬学DDS -DDS製剤と、その薬物治療-] **2019**, Kyoto, Japan: Kyoto hirokawa shoten [京都廣川書店].;
Hashida, M. *Membrane* **1995**, *20*(1), 55-64.; Retrieved from https://www.phar.kyushu-u.ac.jp/lab/gaiyou_10.php

Drug Delivery Systems: Examples

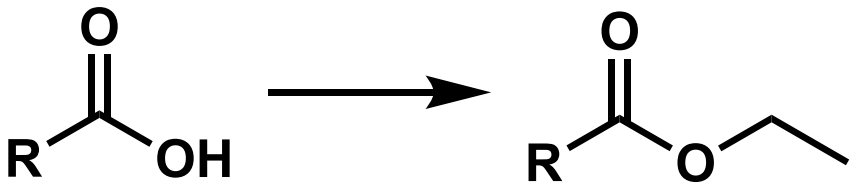
< absorption enhancement >

new administration route



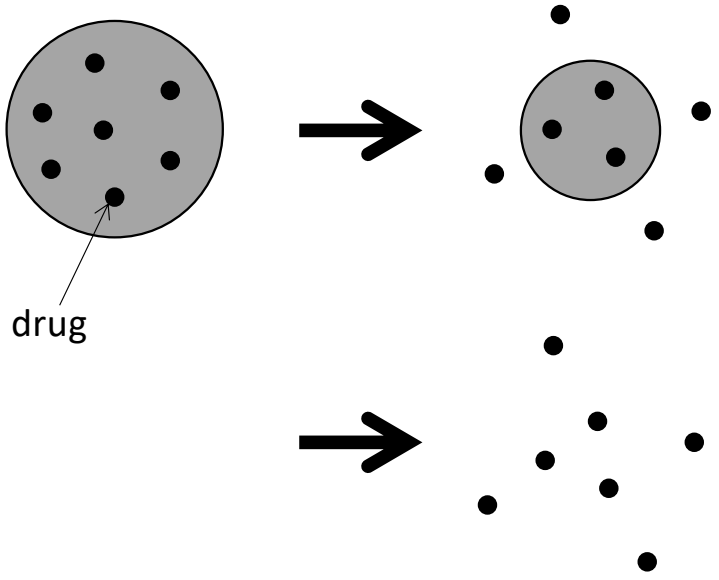
Prodrug

lipid soluble



< controlled release >

sustained release

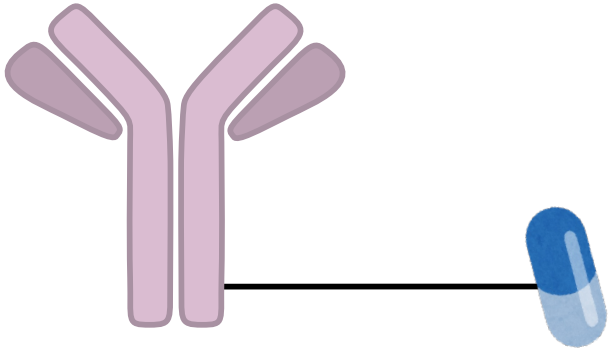


Okamoto, K. *Yakugaku DDS -DDS seizai to sono yakubutsu chiryou-* [薬学DDS -DDS製剤と、その薬物治療-] **2019**, Kyoto, Japan: Kyoto hirokawa shoten [京都廣川書店].

Drug Delivery Systems: Examples

< active targeting >

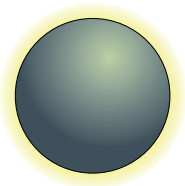
Antibody-Drug Conjugate



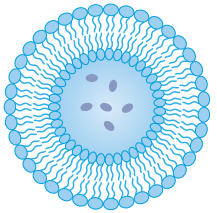
< passive targeting >

nanoparticles

Polymer micelle



Iron oxide NP



Liposome

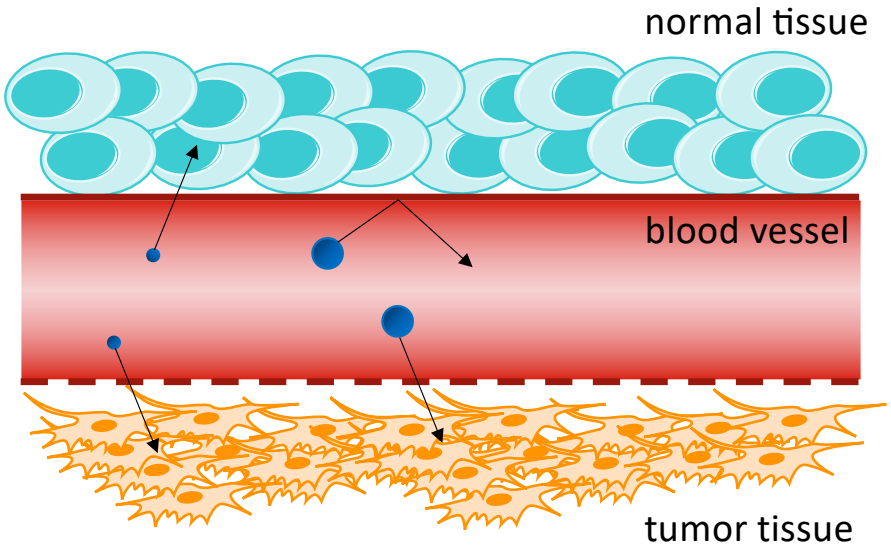
Okamoto, K. *Yakugaku DDS -DDS seizai to sono yakubutsu chiryou-* [薬学DDS -DDS製剤と、その薬物治療-] **2019**, Kyoto, Japan: Kyoto hirokawa shoten [京都廣川書店].;
Mitchell, M. J., Billingsley, M. M., et al. *Nature Reviews Drug Discovery* **2021**, *20*(2), 101–124.

Nanoparticles for Drug Delivery System (DDS)

Advantages of nanoparticles

- improve stability and solubility
- variable drug capacity
- good biocompatibility
- EPR effect
- customizable (surface modification)

Enhanced permeation and retention effect (EPR effect)

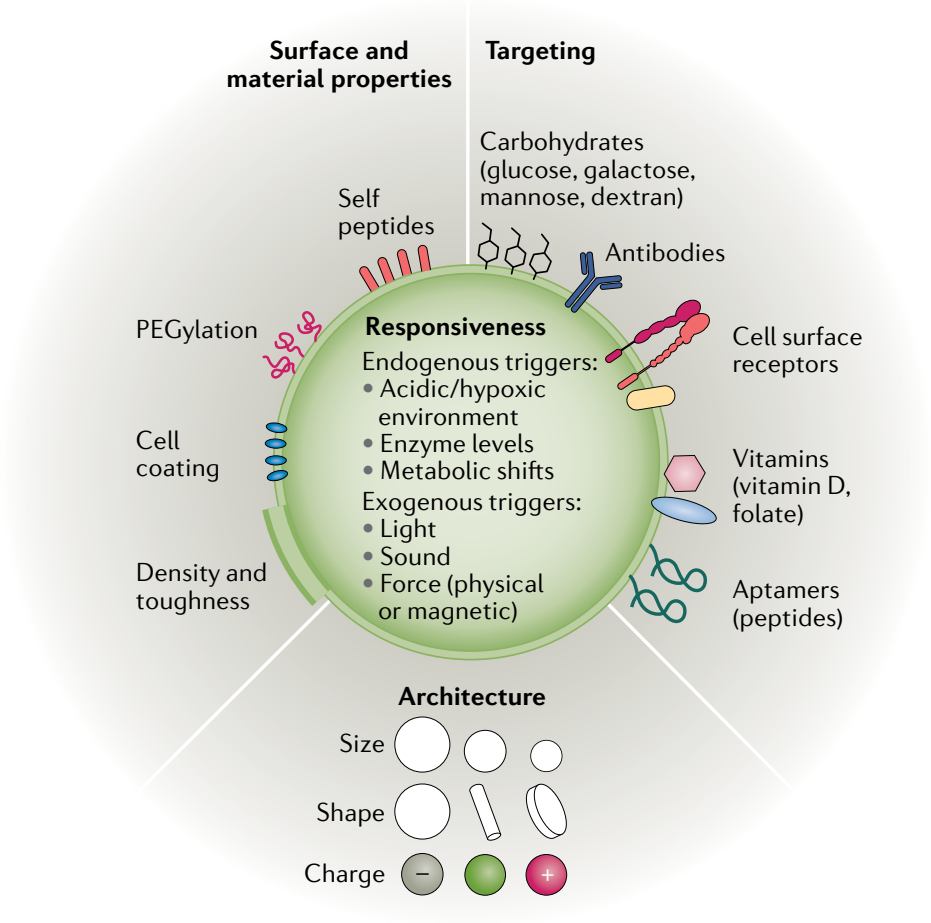


Tagami, T., & Ozeki, T. *Organ Biology* **2017**, *24*(1), 54–60.; Mitchell, M. J., et al. *Nature Reviews Drug Discovery* **2021**, *20*(2), 101–124.; Mousa, S. A., & Bharali, D. J. *Cancers* **2011**, *3*(3), 2888-2903.; Ichikawa, H. *Journal of The Surface Science Society of Japan* **2010**, *31*(10), 543-550.

nanoparticles can change various moieties.

Advantages of nanoparticles

- improve stability and solubility
- variable drug capacity
- good biocompatibility
- EPR effect
- customizable (surface modification)

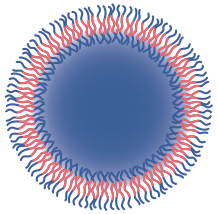


Mitchell, M. J., Billingsley, M. M., et al. *Nature Reviews Drug Discovery* **2021**, *20*(2), 101–124.

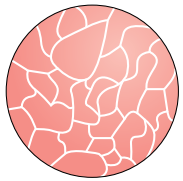
What are nanoparticles?

introduction

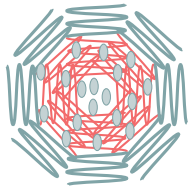
Polymeric



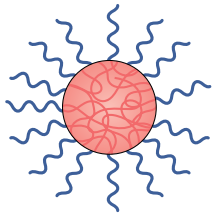
Polymersome



Dendrimer



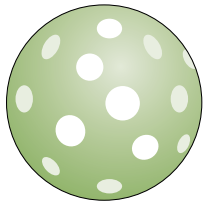
Polymer micelle



Nanosphere

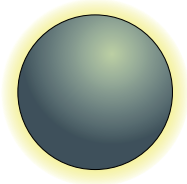
- ✓ biocompatibility
- ✓ precise control of particles
- ✓ easy surface modification
- × possibility for aggregation and toxicity

Inorganic

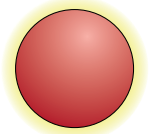


Silica NP

Quantum dot



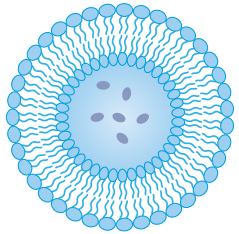
Iron oxide NP



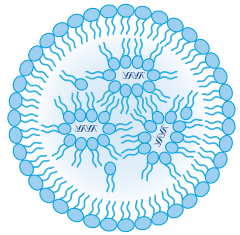
Gold NP

- ✓ unique electrical, magnetic and optimal properties
- ✓ biocompatibility, stability
- × low solubility and toxicity of heavy metal

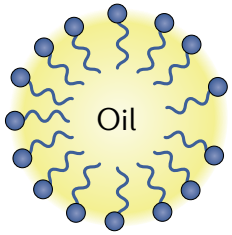
Lipid-based



Liposome



Lipid NP



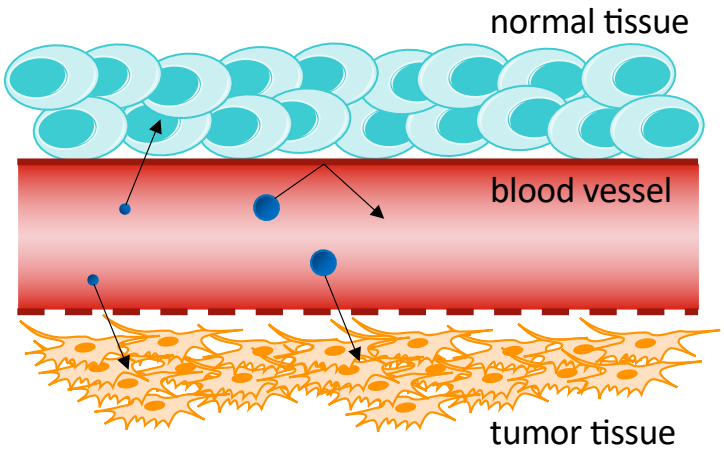
Emulsion

- ✓ formulation simplicity
- ✓ biocompatibility
- ✓ self-assembly
- × low encapsulation efficiency
- × biodistribution

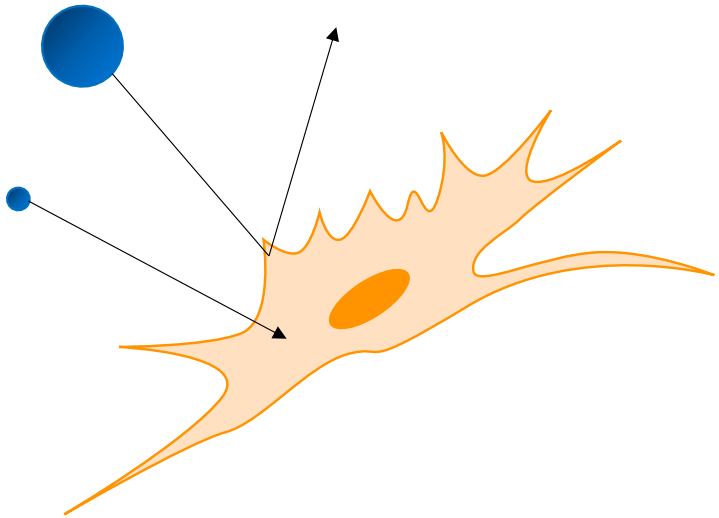
Mitchell, M. J., Billingsley, M. M., et al. *Nature Reviews Drug Discovery* **2021**, *20*(2), 101–124.; Maitani, Y., & Nagai, T. *DDS* **2002**, *17*(4), 314-320.

Introduction: nanoparticle-size-dilemma

large size (20~100nm)
need for EPR effect



small size (~20nm)
need for cell penetration

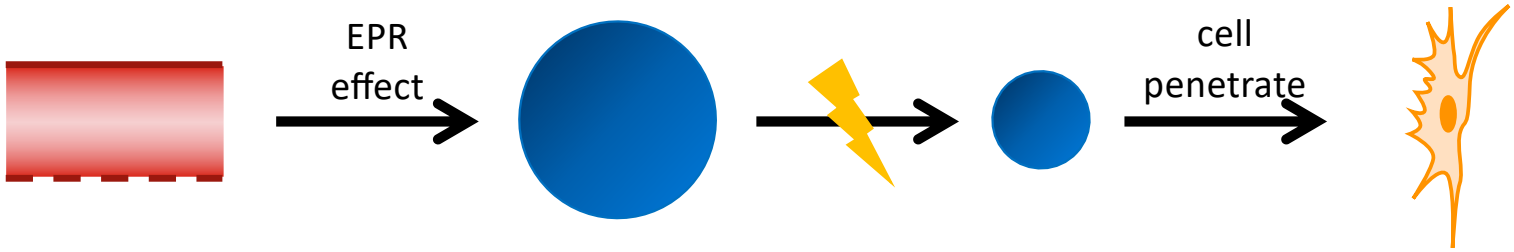


Ichikawa, H. *Journal of The Surface Science Society of Japan* **2010**, *31*(10), 543-550.; Cheng, G., Wu, D., et al. *Nano Today* **2021**, *38*, 101208.

How to shrink the size

- large size until distribution to tumors
- small size after tumor distribution in order to penetrate tumor cells

→ size-change strategy



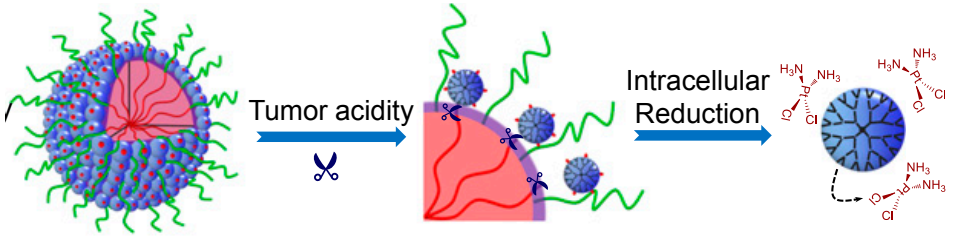
- Trigger of shrinking at only tumor tissues

→use tumor microenvironment or exogenous stimuli

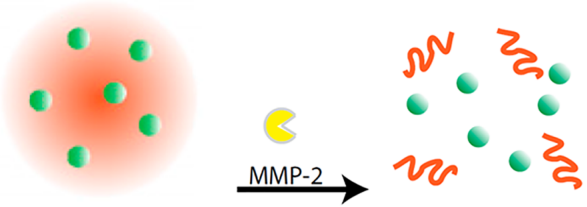
Cheng, G., Wu, D., et al. *Nano Today* **2021**, *38*, 101208.

size-shrinking strategy

pH



enzyme



100 nm QDGelNPs preferentially accumulate in solid tumors by EPR

10 nm QDs can penetrate deep into tumor tissue

redox

light

Li, H., Du, J., et al. *PNAS* **2016**, *113*(15), 4164-4169.; Yu, W., Liu, R., Zhou, Y., & Gao, H. *ACS Central Science* **2020**, *6*(2), 100–116.

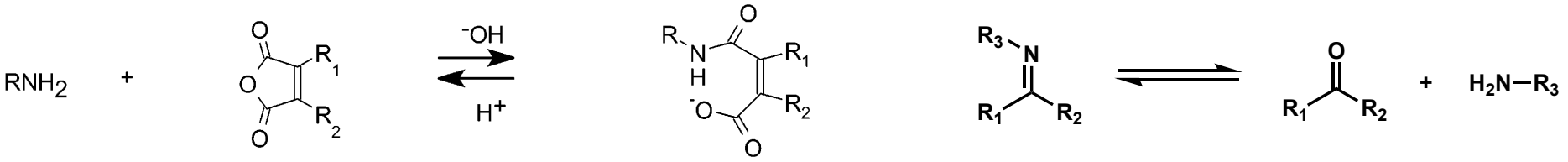
Contents

- Introduction
  - What are Drug Delivery Systems ?
  - What are Nanoparticles ?
  - Current problems
- pH-sensitive size-changeable nanoparticles
  - pH-sensitive linker cleavage type
  - pH-sensitive protonation type
- Summary and perspective

pH-sensitive size-shrinking strategy

research

linker cleavage

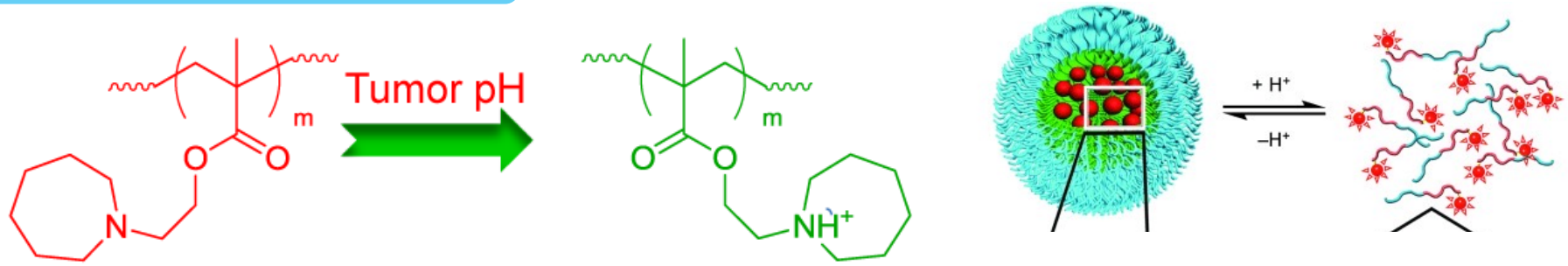


Rozema, D. B., et al. Bioconjugate Chemistry 2003, 14(1), 51–57.

maleamate derivatives

schiff base

amino polymers

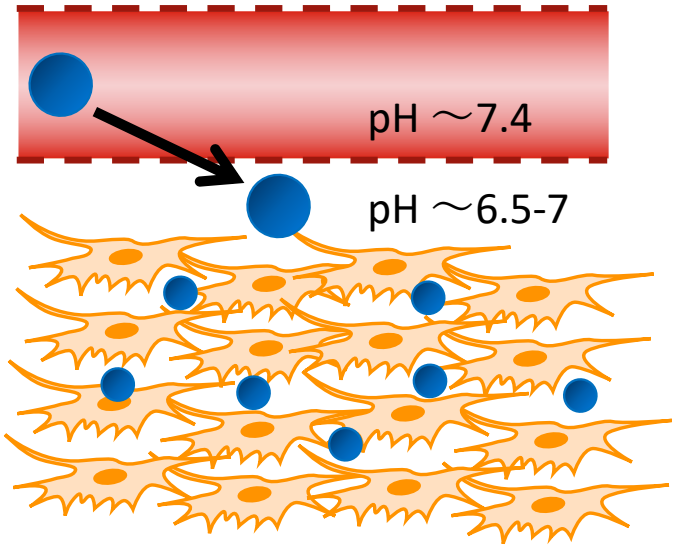


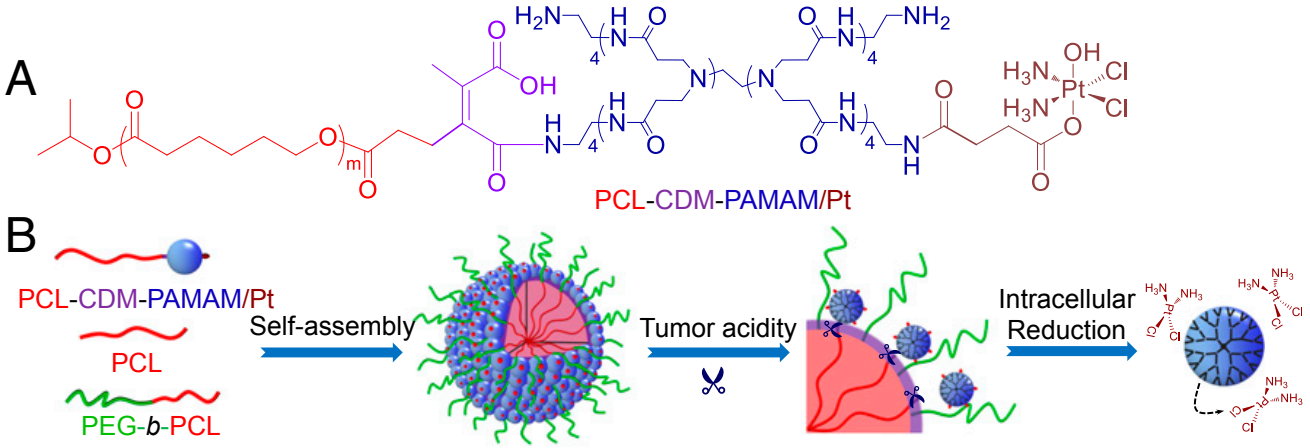
Li, H. J., Du, J. Z., et al. *ACS Nano* **2016**, *10*, 6753−6761.; Yu, W., et al. *ACS Central Science* **2020**, *6*(2), 100–116.; Zhou, K., Wang, Y., et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 6109−6114.

pH-sensitive clustered nanoparticles

research ①

model diagram

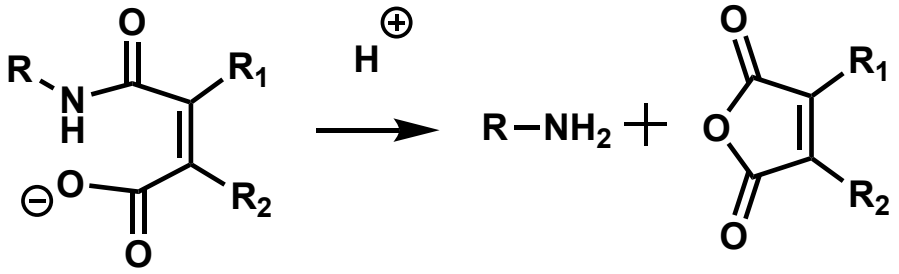


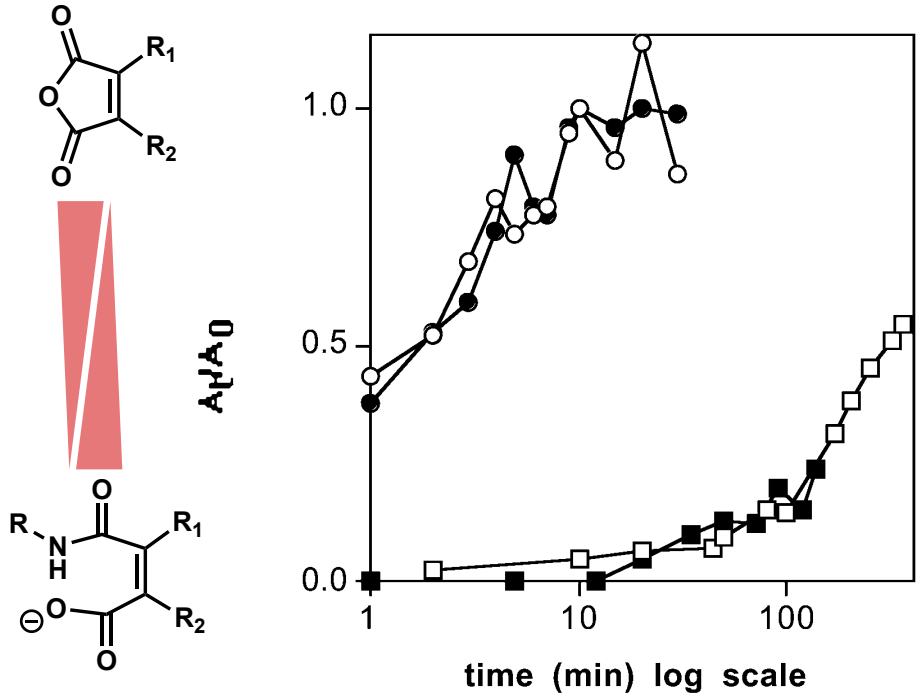


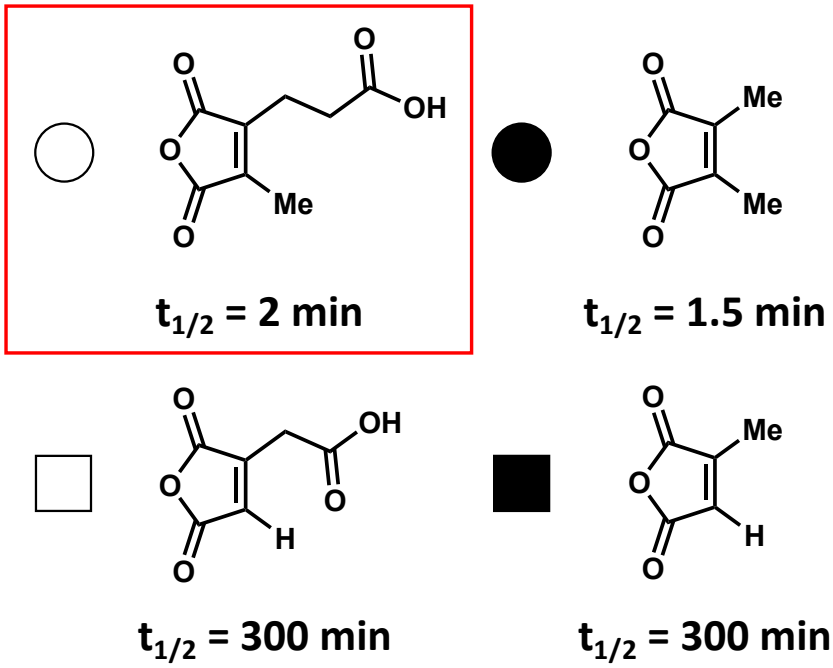
Li, H. J., Du, J. Z., et al. *ACS Nano* **2016**, *10*, 6753−6761.; Li, H., Du, J., et al. *PNAS* **2016**, *113*(15), 4164-4169.

cleavage linker (maleamate derivatives)

research ①





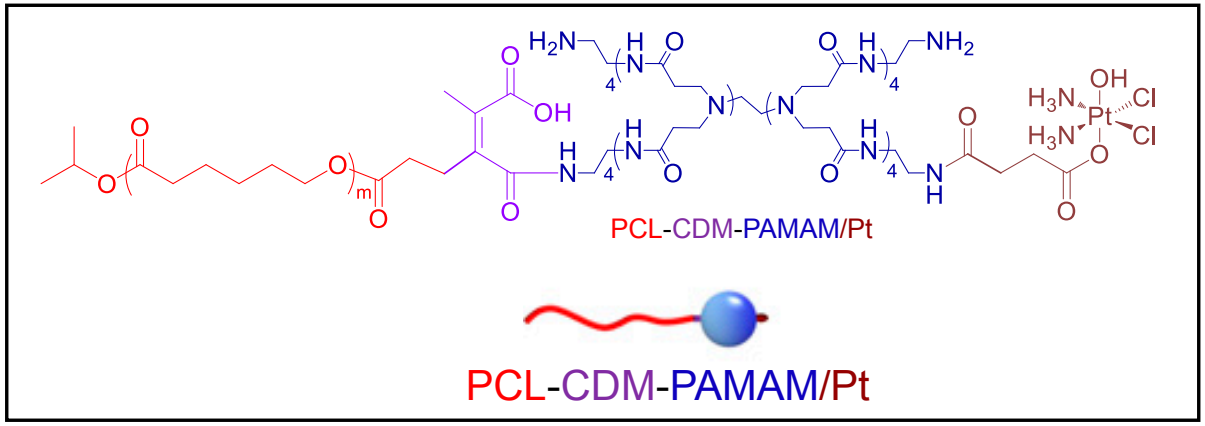


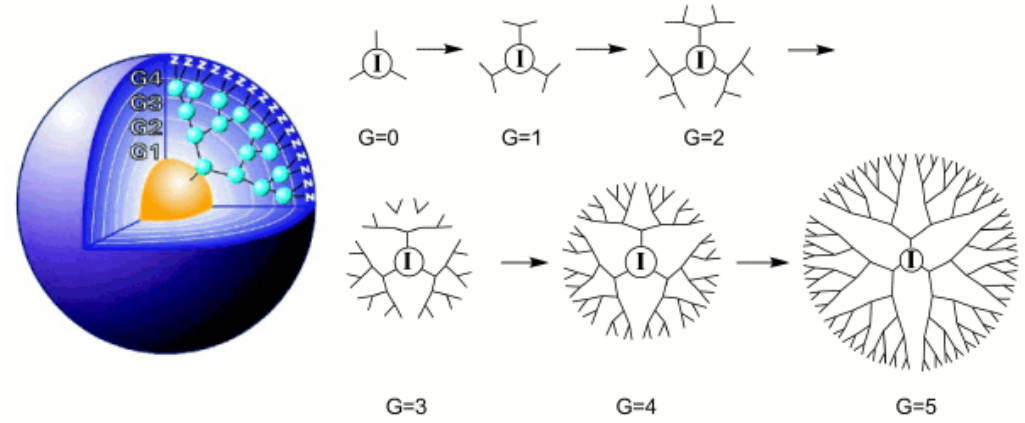
Rozema, D. B., et al. *Bioconjugate Chemistry* **2003**, *14*(1), 51–57.

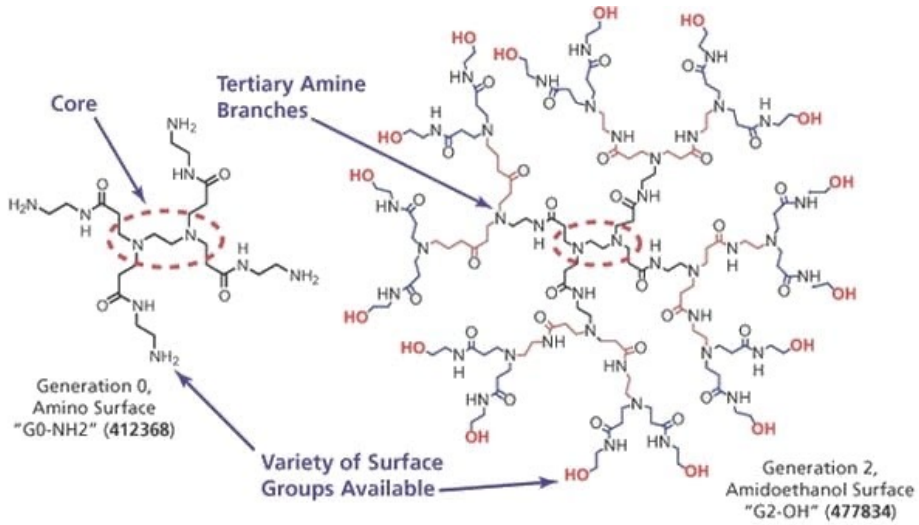
Stimuli-responsive clustered nanoparticles

research ①

- dendrimer
  - highly symmetrical
  - can control size and surface chemistry





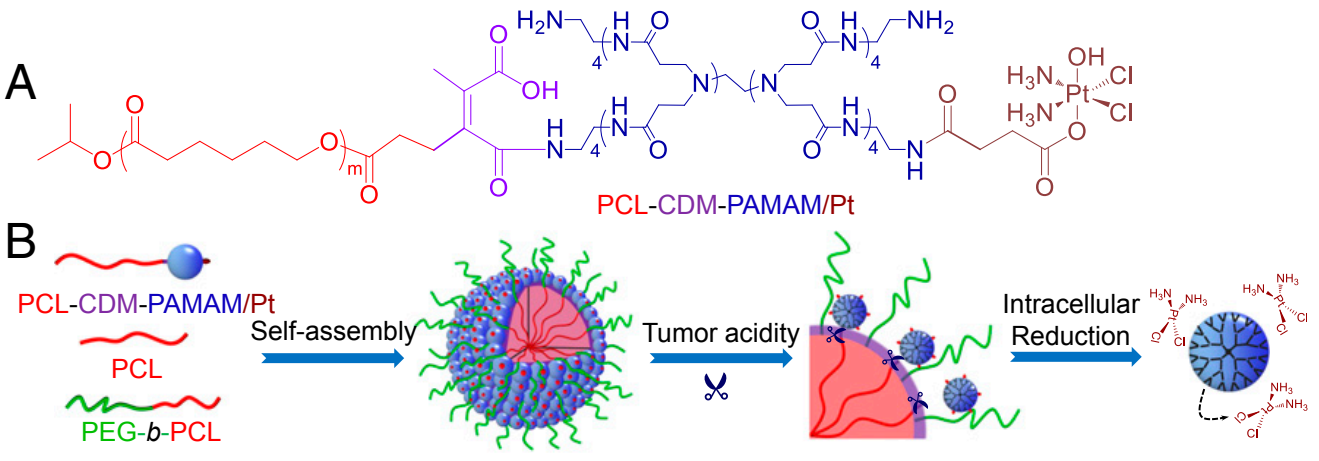


Retrieved from https://www.sigmaaldrich.com/JP/ja/technical-documents/technical-article/materials-science-and-engineering/drug-delivery/dendrimers

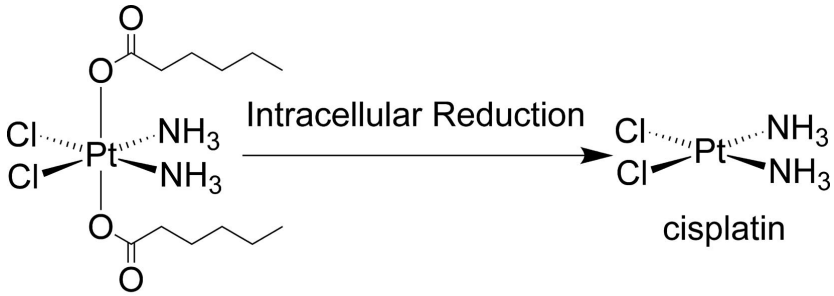
Li, H., Du, J., et al. *PNAS* **2016**, *113*(15), 4164-4169. (Fig. modified)

Stimuli-responsive clustered nanoparticles

research ①



Li, H., Du, J., et al. *PNAS* **2016**, *113*(15), 4164-4169.



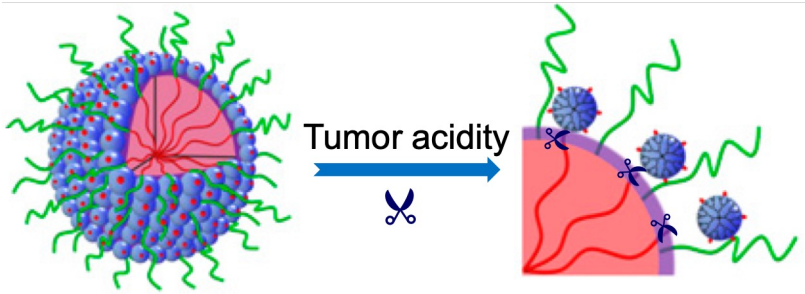
Dhar, S., Gu, FX., et al. *PNAS* **2008**, *105*(45), 17356-17361.

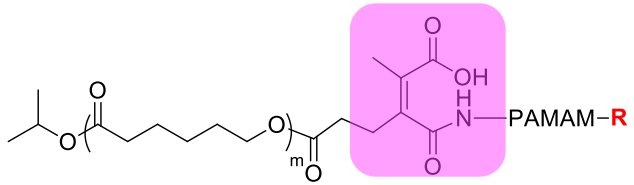
Dhar, S., Daniel, WL., et al. *JACS* **2009**, *131*(41), 14652–14653.; Maitani, Y., & Nagai, T. *Drug Delivery System* **2002**, *17*(4), 314-320.

Nanoparticles which has cleavable linker or not

research ①

iCluster (pH-instable)



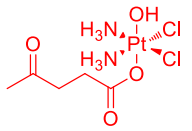


PCL-CDM-PAMAM/Pt

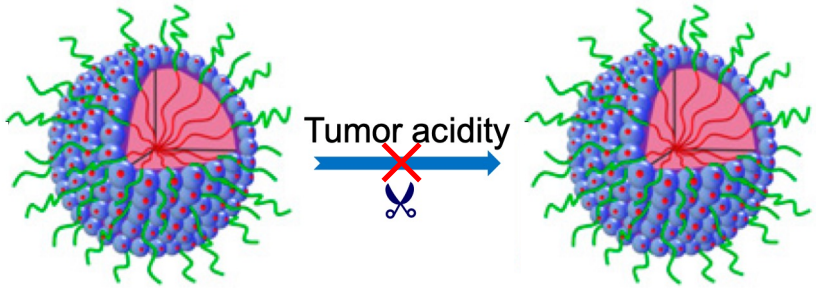
or

PCL-CDM-PAMAM$_{Flu}$

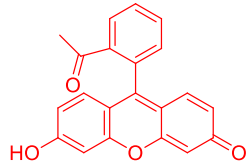
R =

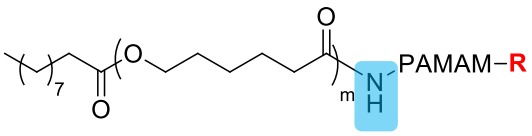


Cluster (pH-stable)



or





PCL-PAMAM/Pt

or

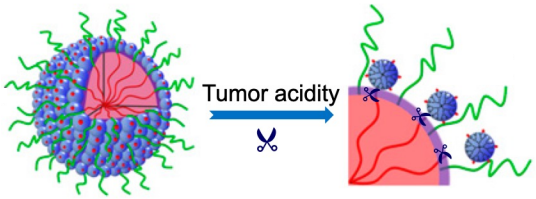
PCL-PAMAM$_{Flu}$

Li, H., Du, J., et al. *PNAS* **2016**, *113*(15), 4164-4169. (Fig. modified)

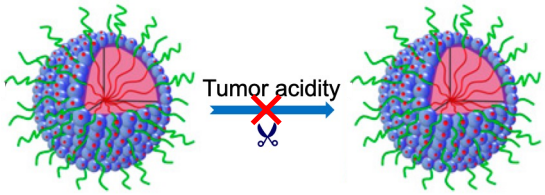
physicochemical properties of the clustered nanoparticles

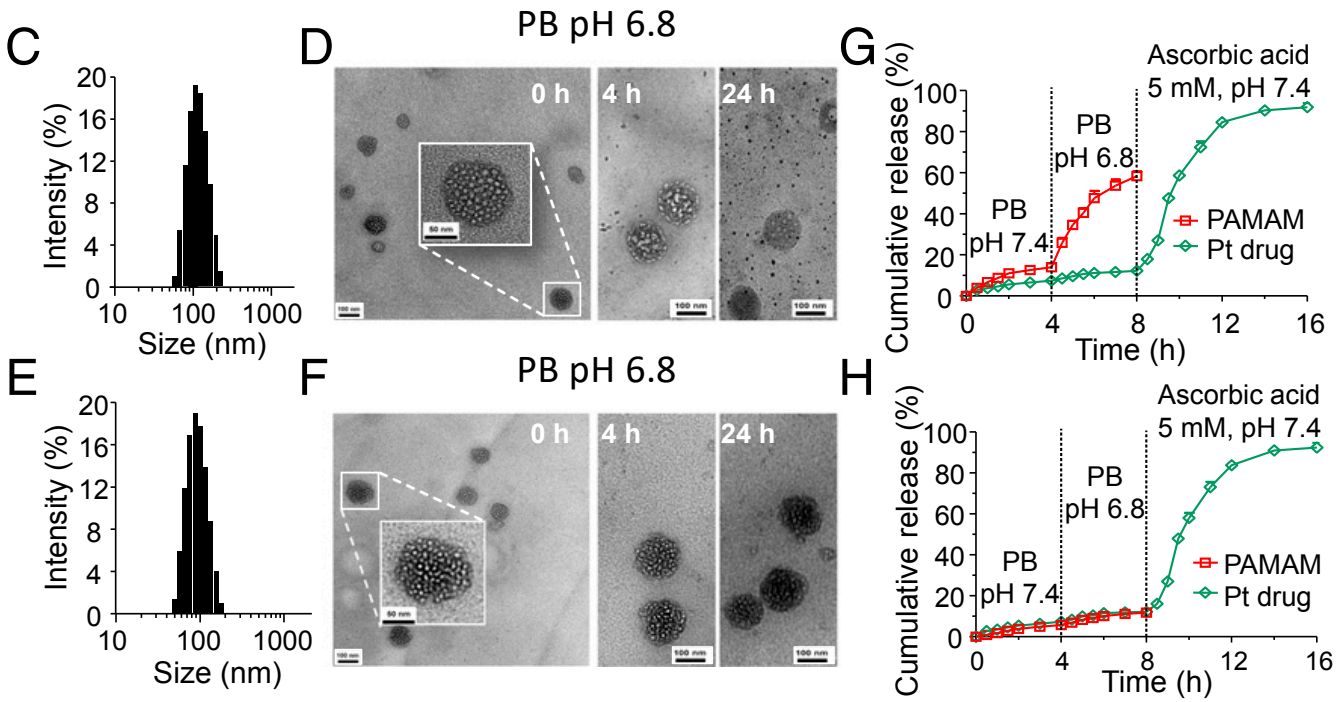
research ①

iCluster (pH-instable)



Cluster (pH-stable)





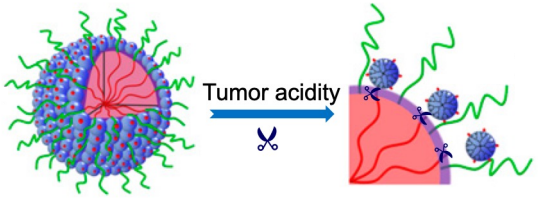
- Each nanoparticle showed similar morphology, size
- plenty of small nanoparticles (PAMAM) were observed after 4h or 24h incubation
- under an intracellular redox environment, both cluster released Pt drugs.

Li, H., Du, J., et al. *PNAS* **2016**, *113*(15), 4164-4169. (Fig. modified)

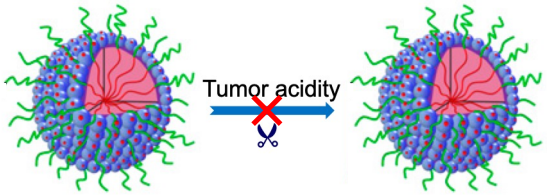
cell penetration and antitumor activity

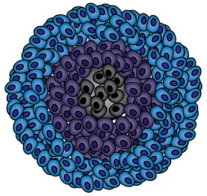
research ①

iCluster (pH-instable)



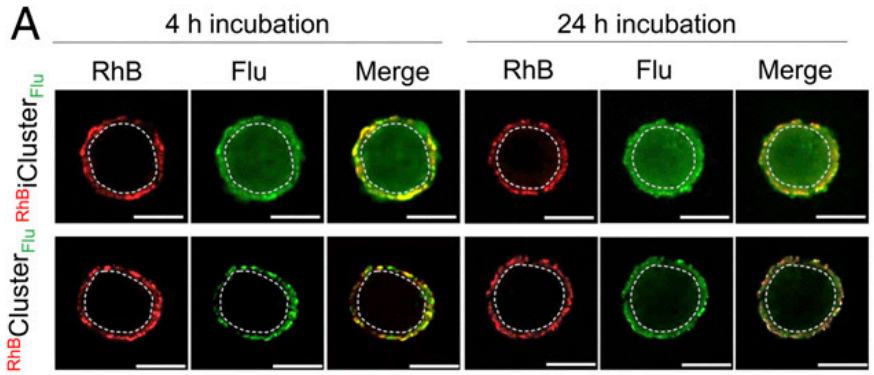
Cluster (pH-stable)

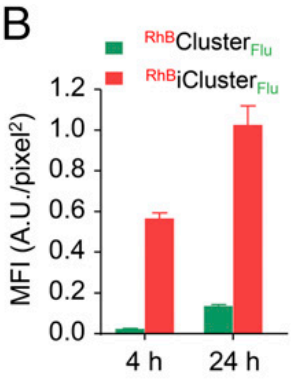




3D-model of cancer

in cell





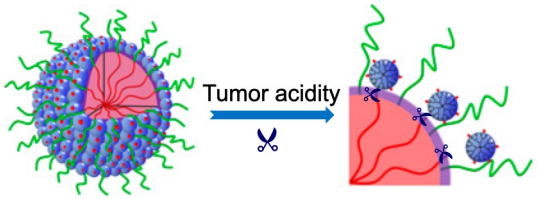
large nanoparticles (RhB), PAMAM dendrimers (Flu)

- The size-changeable iCluster had better tumor penetration
- Compared with Cluster/Pt, iCluster/Pt exhibited significant suppression of tumor growth

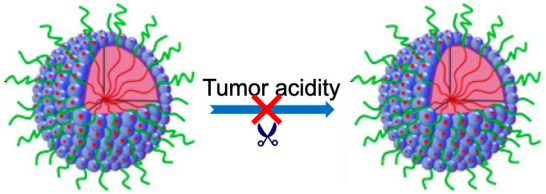
Li, H., Du, J., et al. *PNAS* **2016**, *113*(15), 4164-4169.; Kamatur, A., et al. *Polymers* **2020**, *12*(11), 2506.

cell penetration and antitumor activity

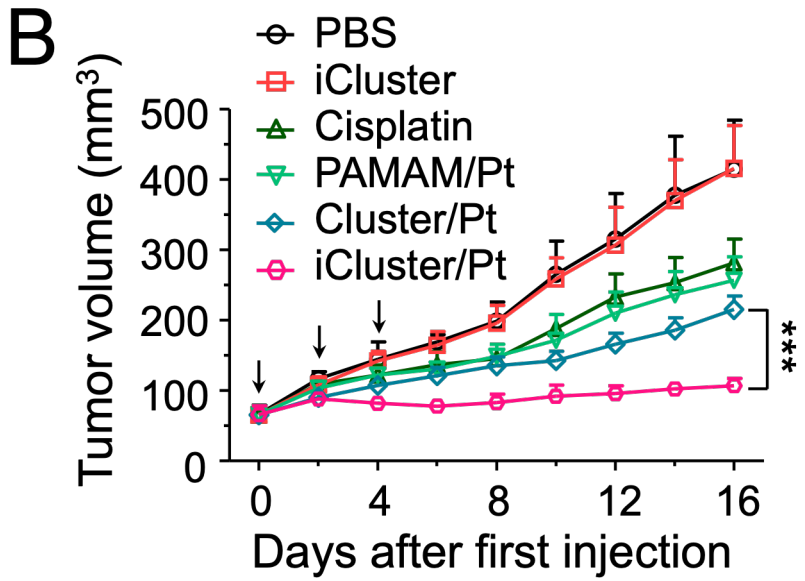
iCluster (pH-instable)



Cluster (pH-stable)



in vivo

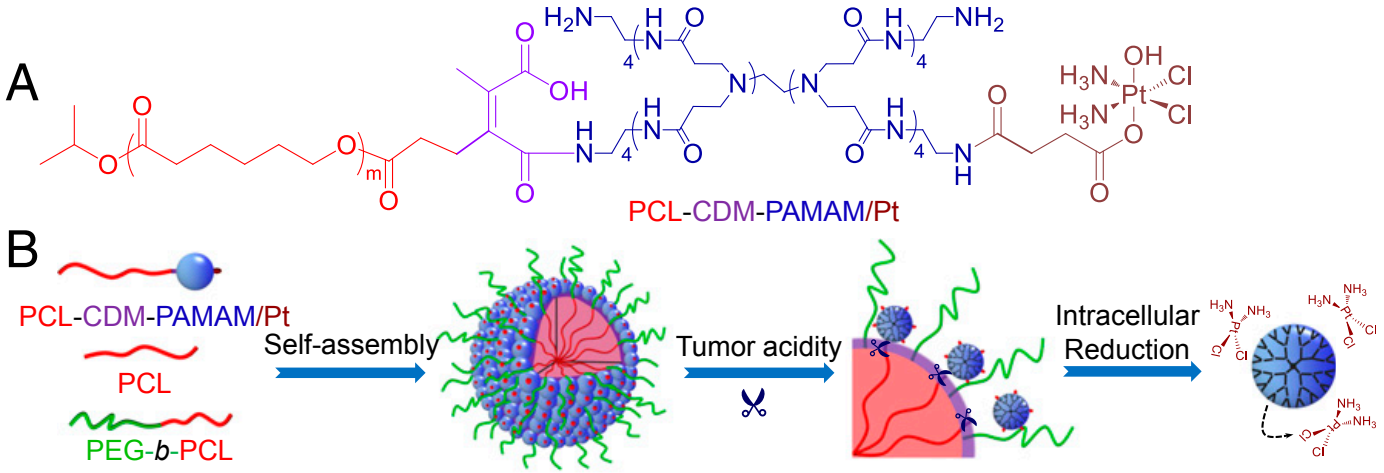


- The size-changeable iCluster had better tumor penetration
- Compared with Cluster/Pt, iCluster/Pt exhibited significant suppression of tumor growth

Li, H., Du, J., et al. *PNAS* **2016**, *113*(15), 4164-4169.

Short summary

research ①



✓iCluster system enables that robust tumor penetration achieved through pH-triggered shattering of small PAMAM dendrimers at tumor sites

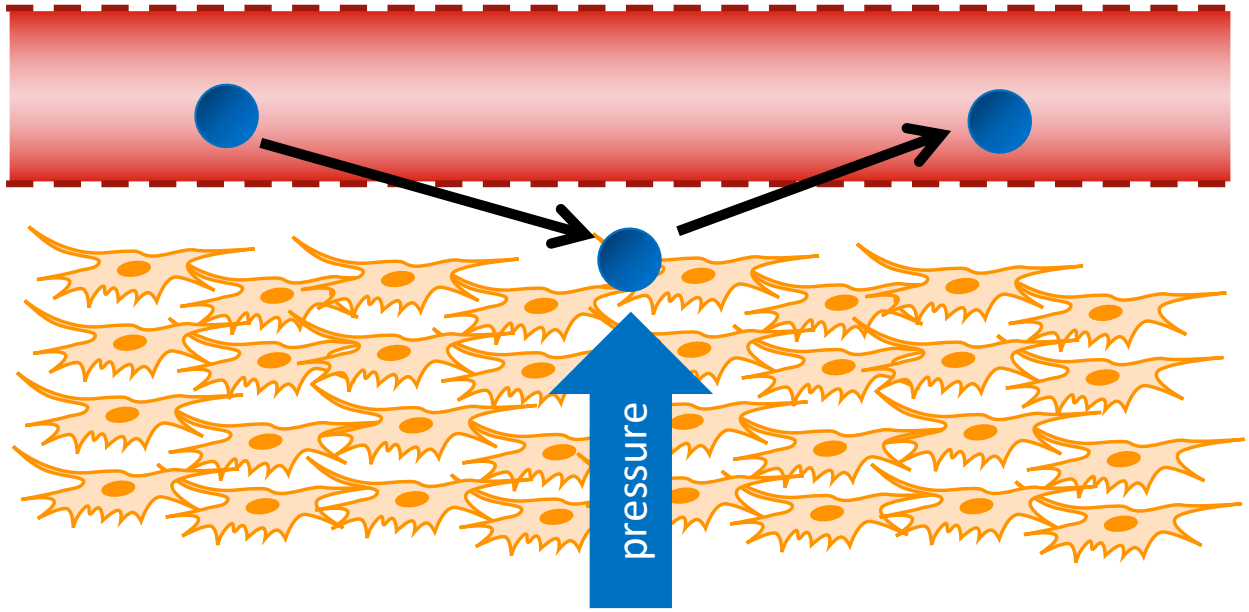
✓exhibited significant antitumor activity

× take much time to complete the transition ($t_{1/2}$ = 2min)

Li, H., Du, J., et al. *PNAS* **2016**, *113*(15), 4164-4169.

take much time to complete the transition

research ①→②

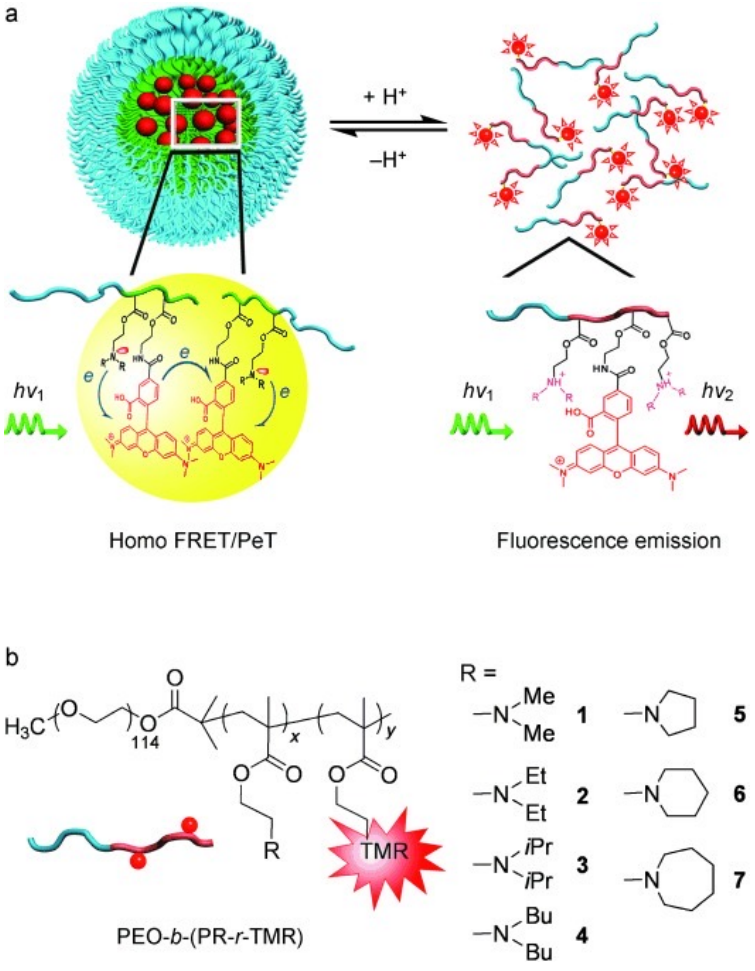


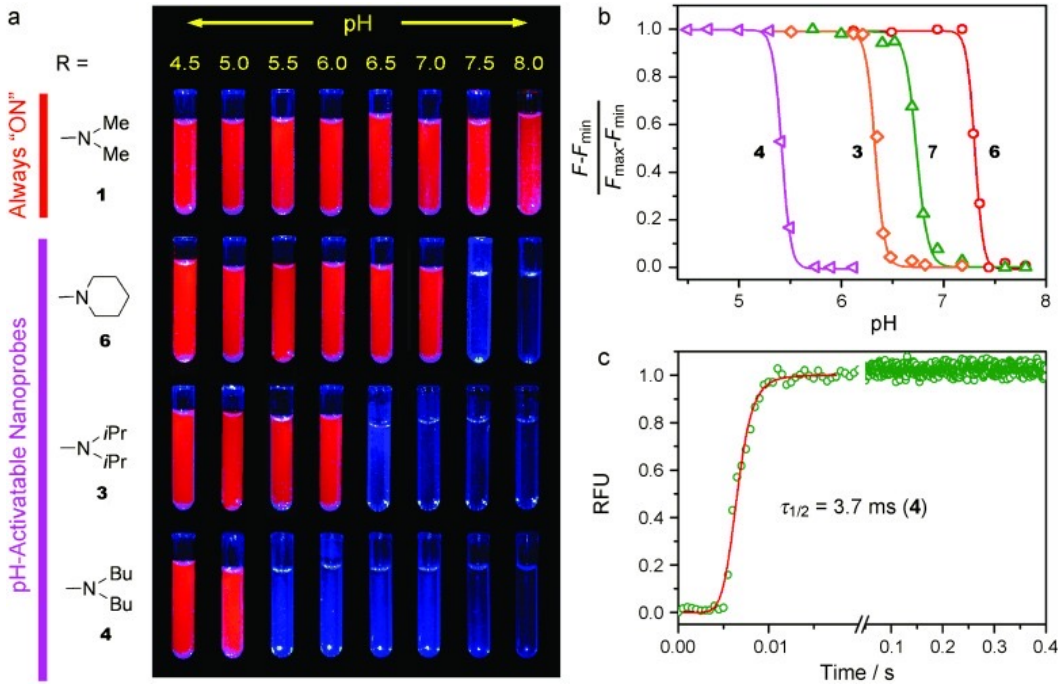
- high interstitial fluid pressure typically prevent permeation of nanoparticles
- easily pumped back to vessels

Cheng, G., Wu, D., et al. *Nano Today* **2021**, *38*, 101208.; Mitchell, M. J., Billingsley, M. M., et al. *Nature Reviews Drug Discovery* **2021**, *20*(2), 101–124.; Wong, C., Stylianopoulos, T., et al. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 2426−2431. Yu, W., Liu, R., Zhou, Y., & Gao, H. *ACS Central Science* **2020**, *6*(2), 100–116.

ultra-pH-sensitive and fast reactivity site

research ①→②



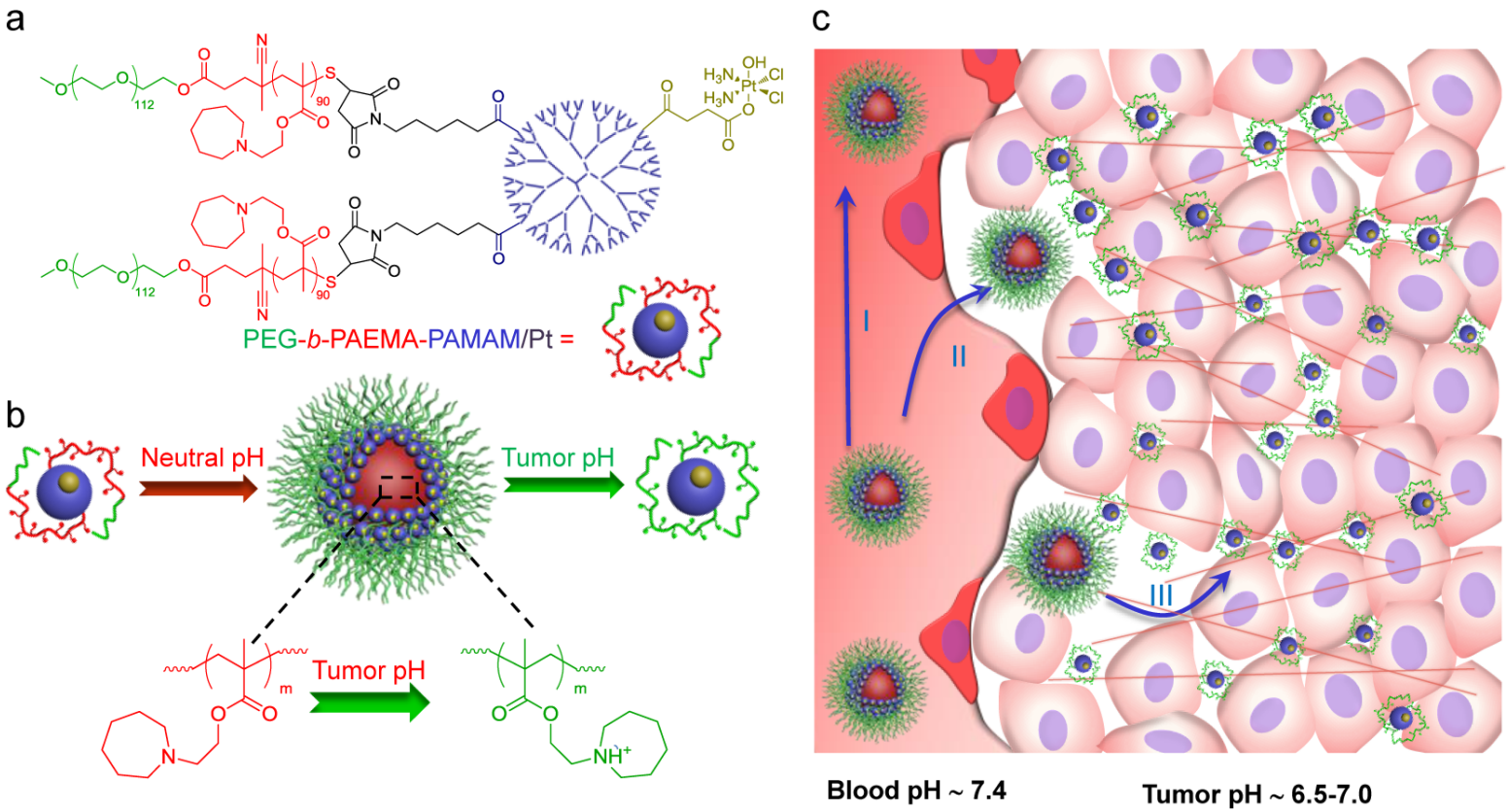


- 2-(Hexamethyleneimino)ethyl group was the best.

Zhou, K., Wang, Y., et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 6109−6114.

improved nanoparticle design

research ②



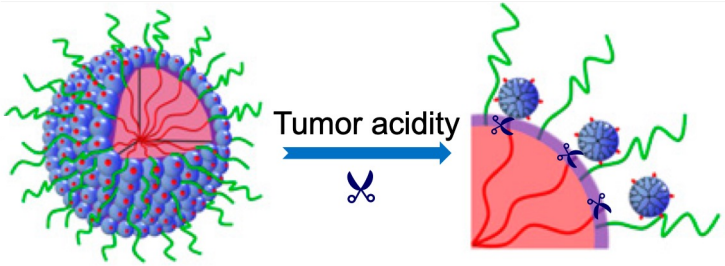
➢ pH sensitive nanoparticle was improved

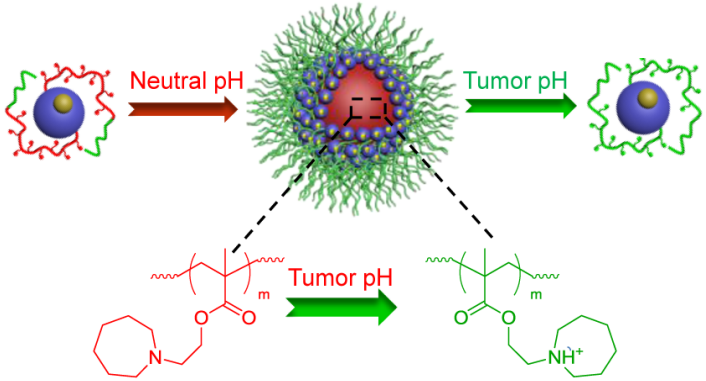
Li, H. J., Du, J. Z., et al. *ACS Nano* **2016**, *10*, 6753−6761.

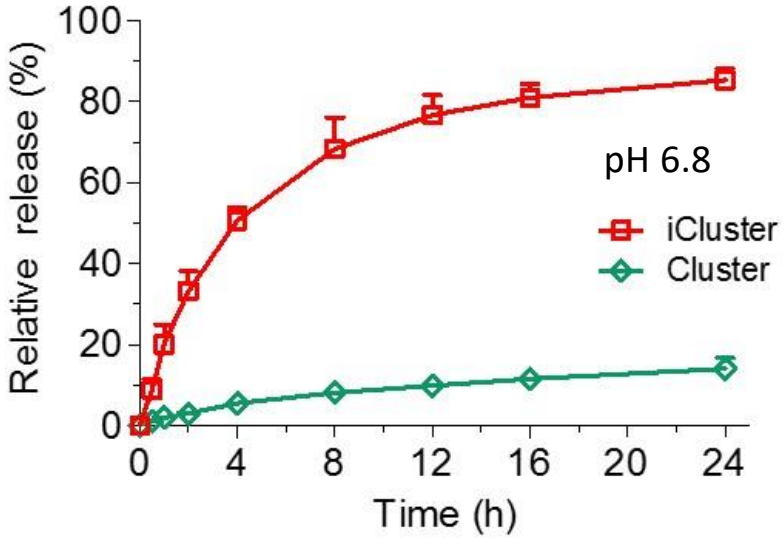
protonation type reacted faster

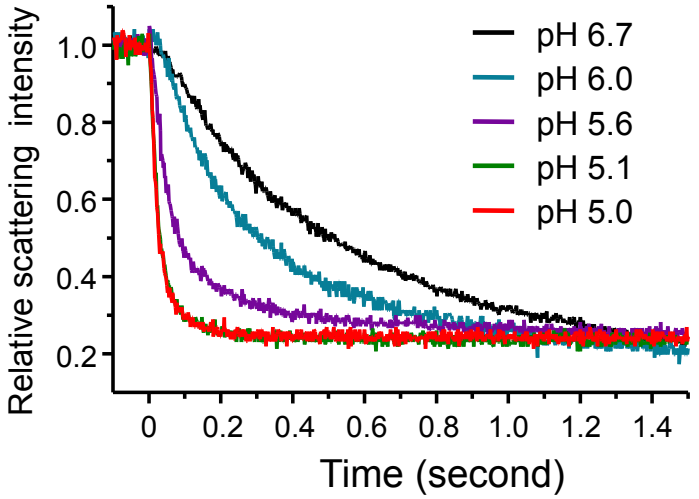
research ②

iCluster (pH-instable)







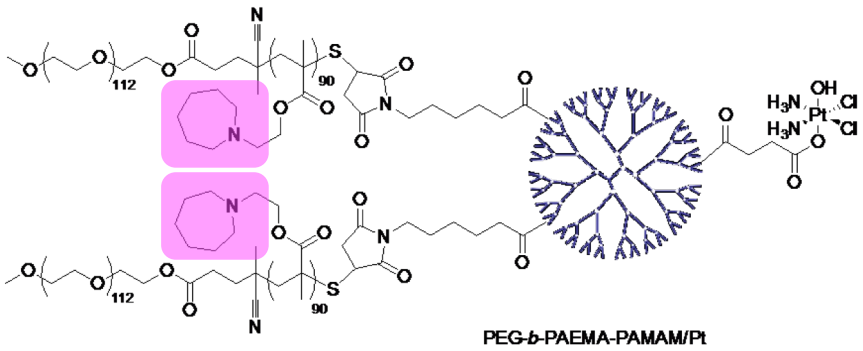


Li, H. J., Du, J. Z., et al. *ACS Nano* **2016**, *10*, 6753−6761.; Li, H., Du, J., et al. *PNAS* **2016**, *113*(15), 4164-4169. (Fig. modified)

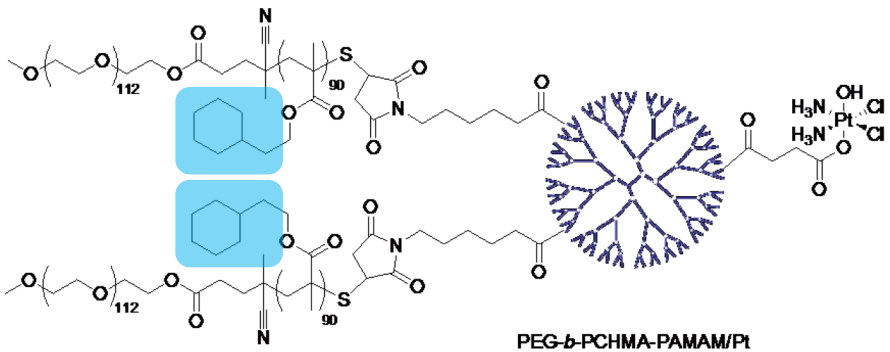
SCN and ICN

research ②

SCN (pH-sensitive cluster nanostructure)



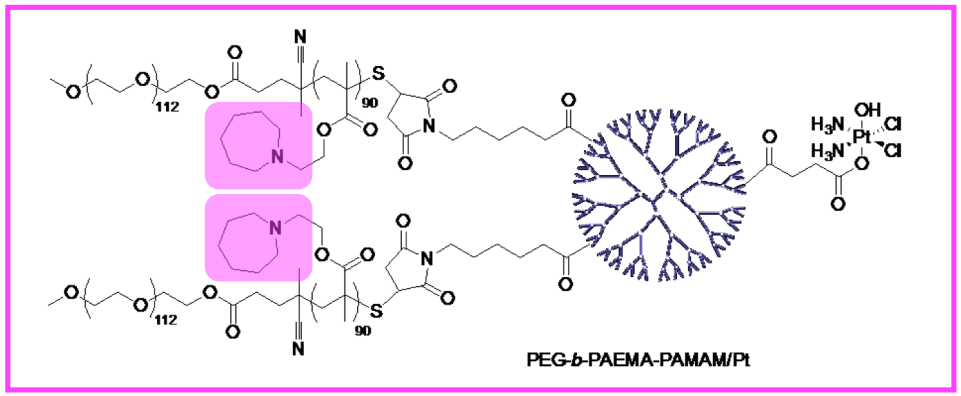
ICN (pH-insensitive cluster nanostructure)

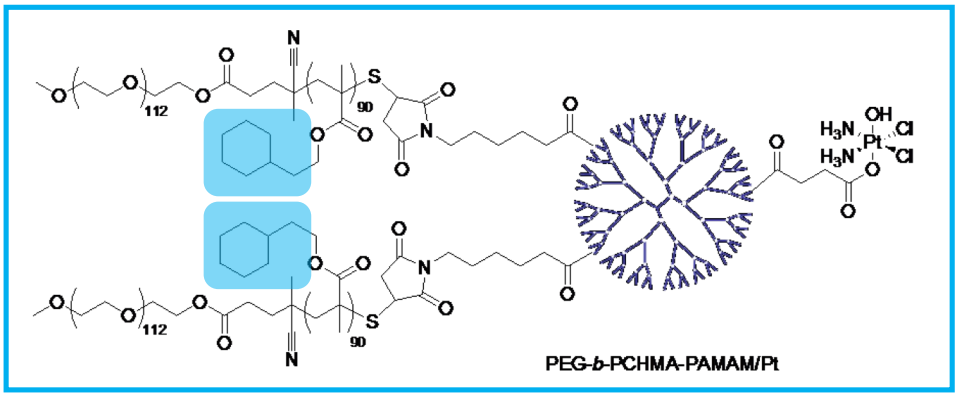


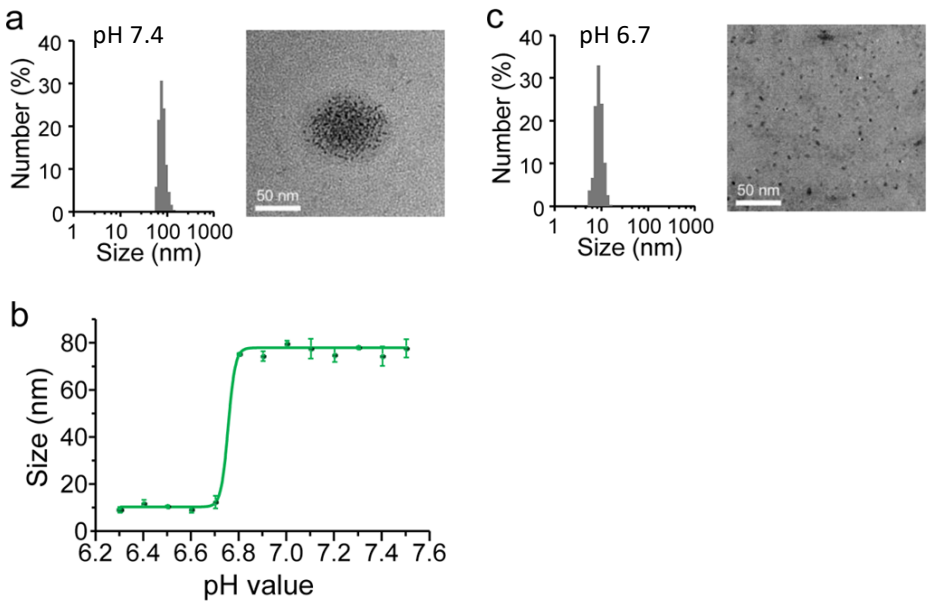
Li, H. J., Du, J. Z., et al. *ACS Nano* **2016**, *10*, 6753−6761. (Fig. modified)

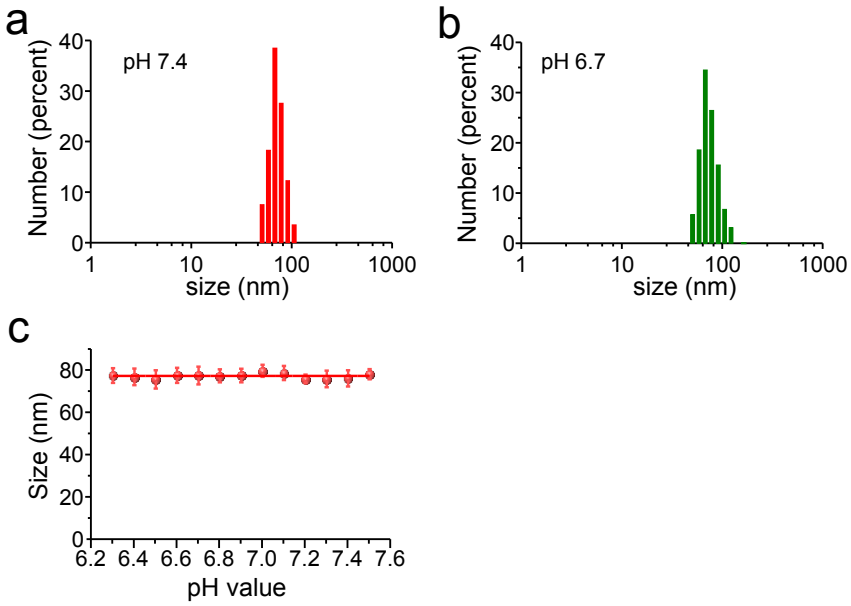
Tumor-pH-triggered size transition of SCNs/Pt.

research ②





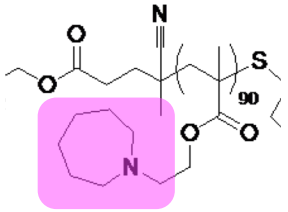




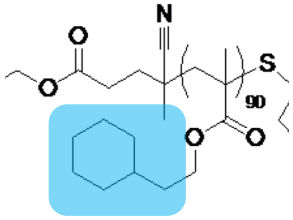
Li, H. J., Du, J. Z., et al. *ACS Nano* **2016**, *10*, 6753−6761. (Fig. modified)

penetration of SCNs/Cy5 and ICNs/Cy5

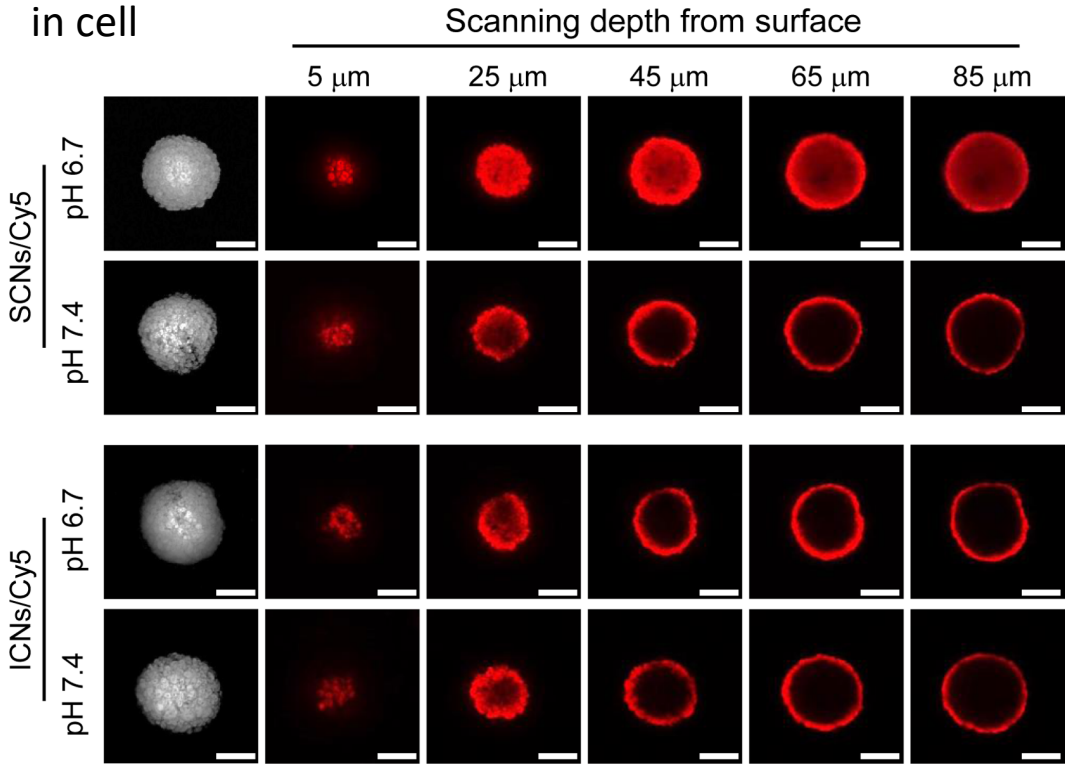
research ②

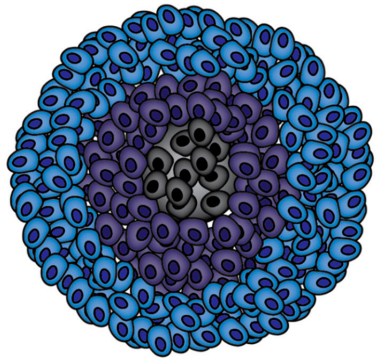


SCNs
(pH-sensitive)



ICNs
(pH-insensitive)





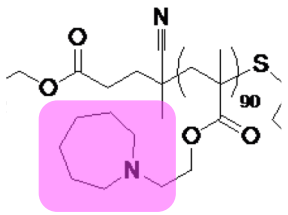
3D-model of cancer

➢ The robust penetration of SCNs/Cy5 at acidic pH

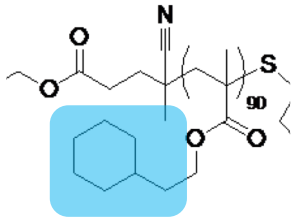
Li, H. J., Du, J. Z., et al. *ACS Nano* **2016**, *10*, 6753−6761.; Lin, R. Z., & Chang, H. Y. *Biotechnology Journal* **2008**, *3*(9–10), 1172–1184.

tumor penetration and antitumor activity study

research ②

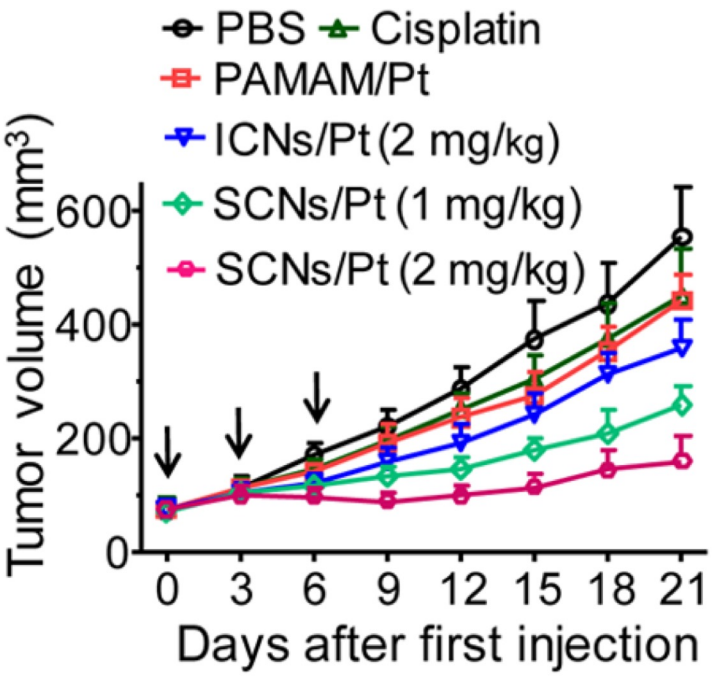


SCNs
(pH-sensitive)



ICNs
(pH-insensitive)

in vivo



➢ SCNs/Pt was effective in suppressing tumor growth

Li, H. J., Du, J. Z., et al. *ACS Nano* **2016**, *10*, 6753−6761.

Contents

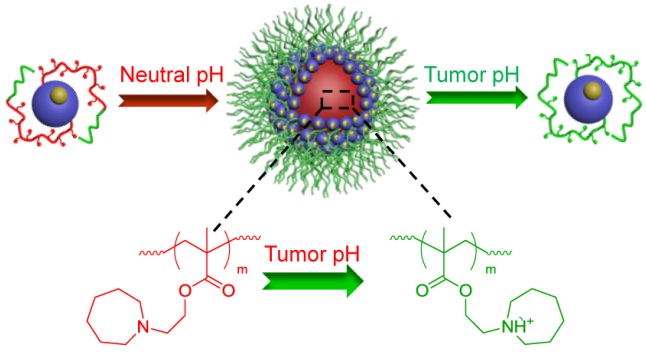
Summary

➢Summary

✓the problem of nanoparticles for DDS is size-dilemma
large size for EPR effect ↔ small size for penetration
→ size-change strategy

✓pH-sensitive and rapid reactive size-changeable nanoparticle was designed

✓great tumor penetration and antitumor activity



Li, H. J., Du, J. Z., et al. *ACS Nano* **2016**, *10*, 6753−6761.

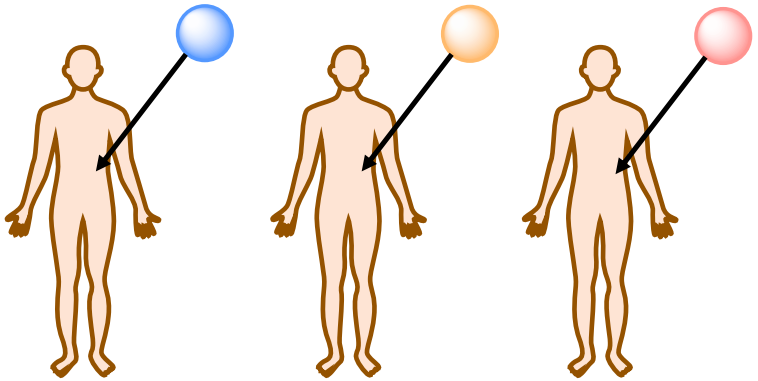
Problems and Perspectives

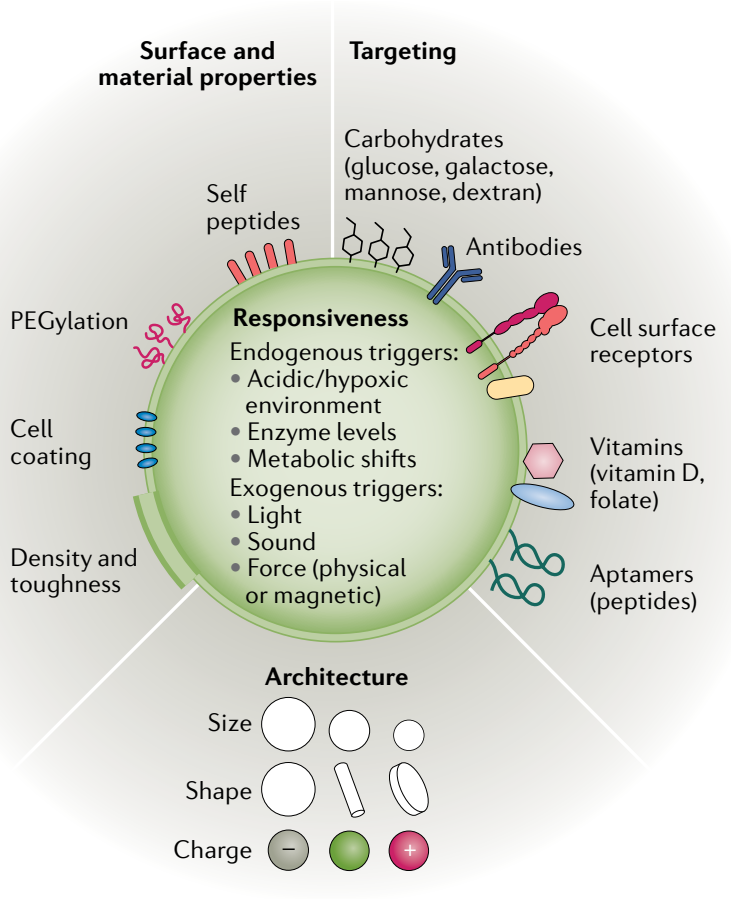
- Problems
  - off-target of EPR effect (liver, Spleen, etc.)
  - cell penetration
  - complicated tumor microenvironment
  - retention time → size-increasing strategy
  - toxicity (antigenicity, slow elimination)
  - protein corona
  - translational gap

Yu, W., Liu, R., Zhou, Y., & Gao, H. *ACS Central Science* **2020**, *6*(2), 100–116.; Blanco, E., Shen, H., & Ferrari, M. *Nature Biotechnology* **2015**, *33*(9), 941–951.; Yokoyama, M. *Drug Delivery System* **2018**, *33*(2), 89–97.; Zanganeh, S., Spitler, R., et al. *International Journal of Biochemistry and Cell Biology* **2016**, *75*, 143–147.

Problems and Perspectives

- Perspectives
  - combination of modification
  - Precision medicine





Mitchell, M. J., Billingsley, M. M., et al. *Nature Reviews Drug Discovery* **2021**, *20*(2), 101–124.