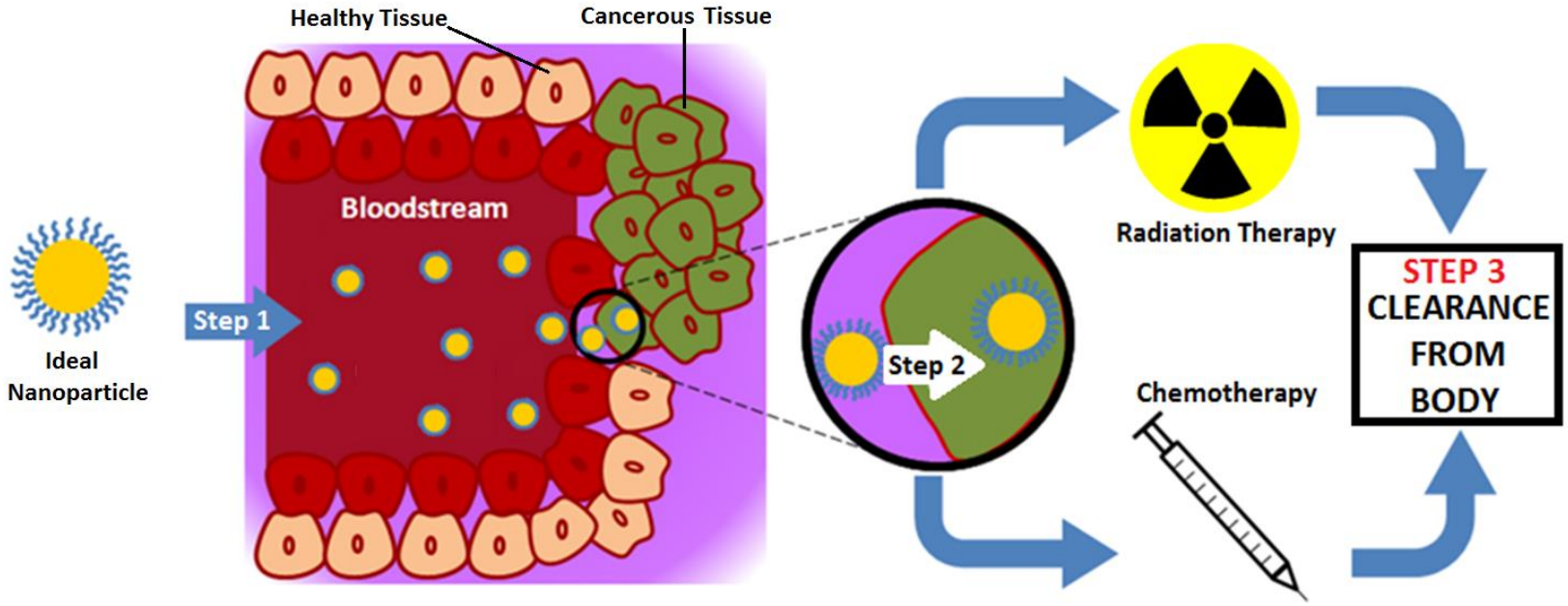
Effect of pegylated gold nanoparticle core size on cancer cell uptake



By Charmainne Cruje

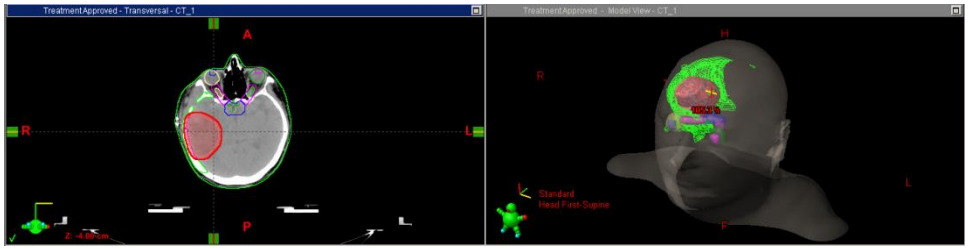
Ryerson University

Supervised by Dr. Devika B. Chithrani

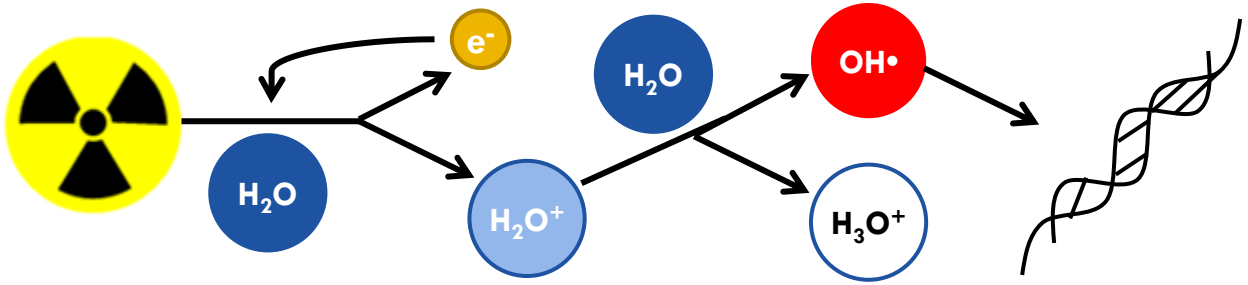
Radiation Therapy Cancer Treatment

- Target organs versus organs at risk
- Set dose limits
- Software optimization

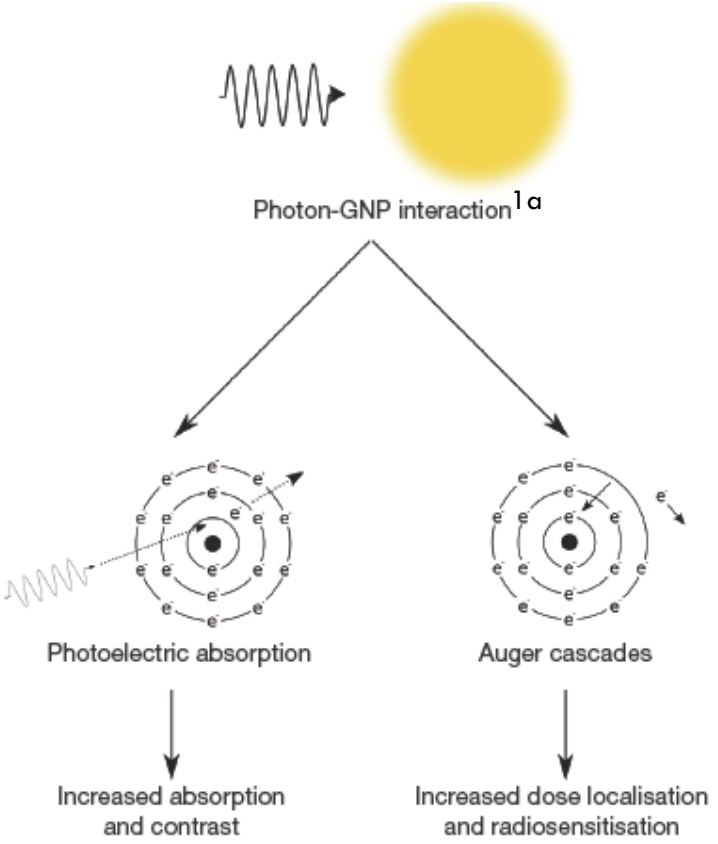
Target Organ and Healthy Organs



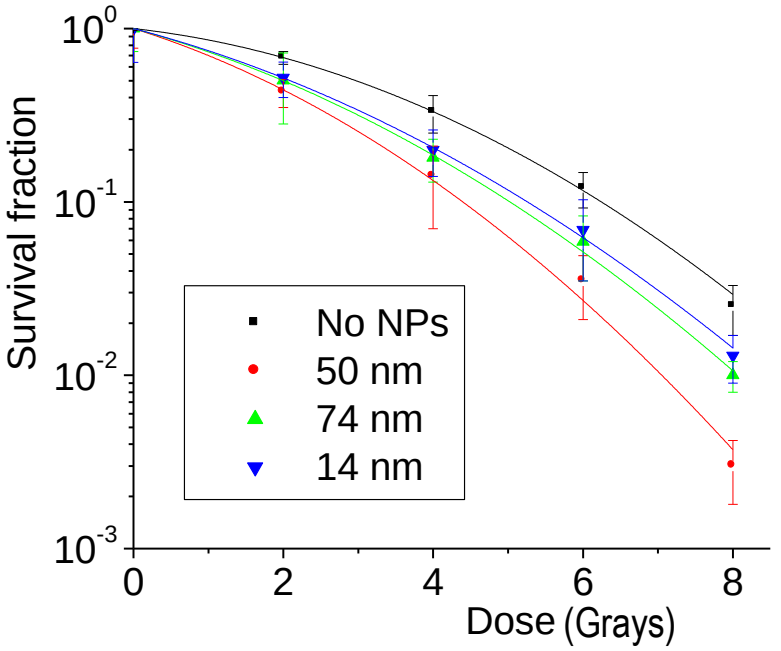
Radiation Cell Killing Process



Gold Nanoparticles (NPs) as Radiosensitizers



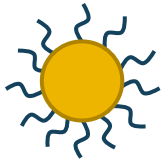
Radiation Therapy and Gold NP Treatment of Cultured Cervical Cancer Cells[1b]



[1a]Butterworth KT, McMahon SJ, Taggart LE, Prise KM, Radiosensitization by Gold Nanoparticles: Effective at Megavoltage Energies and Potential Role of Oxidative Stress, Transl. Cancer Res., 2013;2(4):269-279.

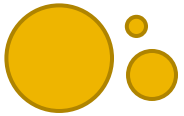
[1b]Chithrani DB, Jelveh S, Jalali F, Van Prooijen M, Allen C, Bristow RG, Hill RP, Jaffray DA, Gold Nanoparticles as Radiation Sensitizers in Cancer Therapy, Radiat Res, 2010;173:719-728.

Advantages of Gold NPs

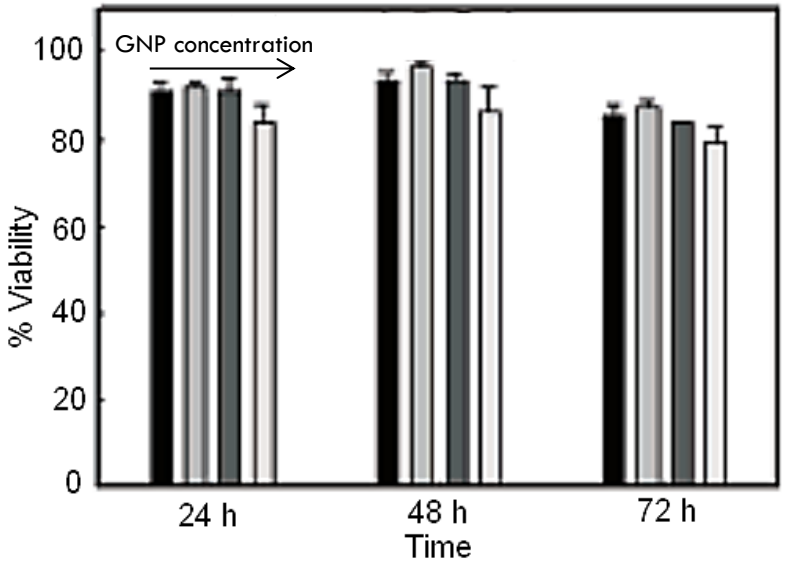


Ease of Design
Conjugation

Gold NPs



Ease of Synthesis
Ideal Model Nanoparticle System to Improve Bio-Nano Interface

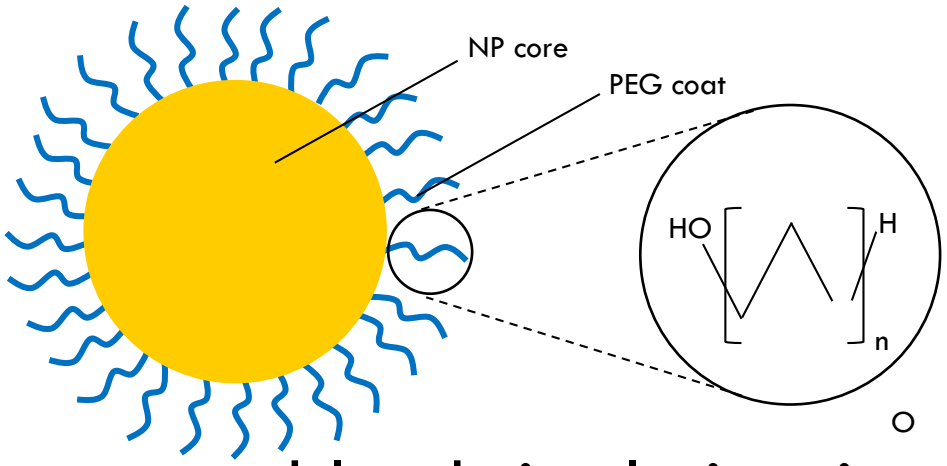


Biocompatibility[2]

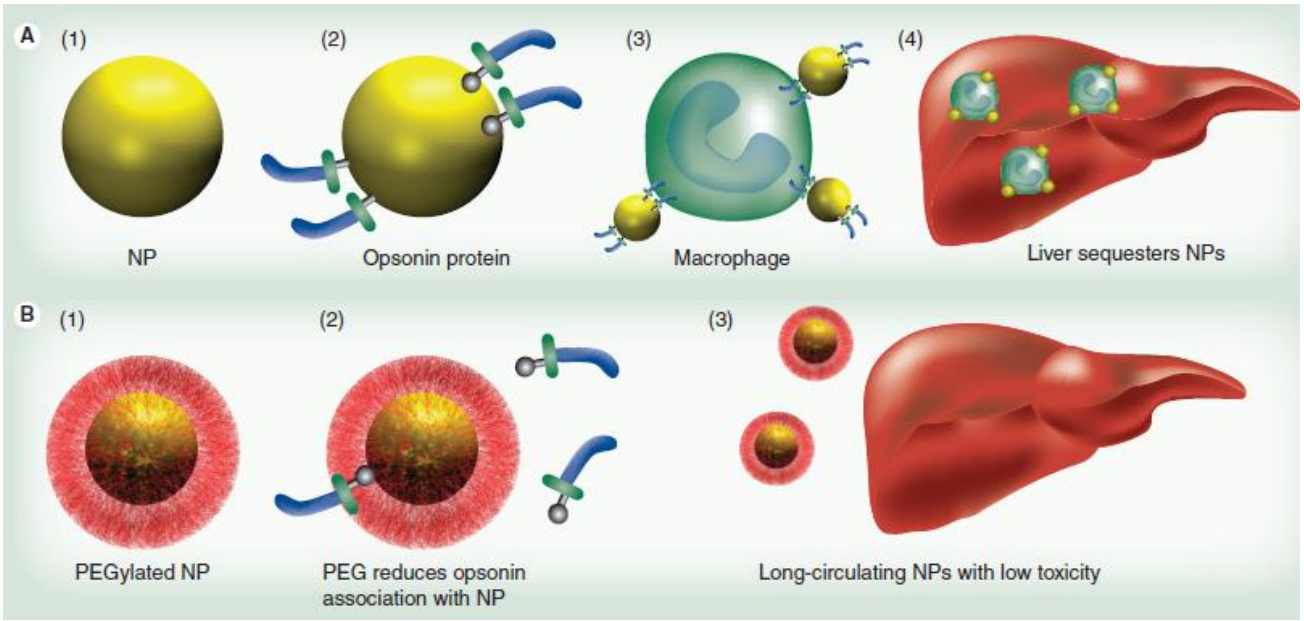
- Immune system cells in vitro
- 3.5 ± 0.7 nm Gold NPs

[2]Shukla, R., Bansal, V., Chaudhary, M., Basu, A., Bhonde, R. R., & Sastry, M. (2005). Biocompatibility of gold nanoparticles and their endocytotic fate inside the cellular compartment: A microscopic overview. *Langmuir : The ACS Journal of Surfaces and Colloids, 21*(23), 10644-10654.

Polyethylene glycol (PEG)



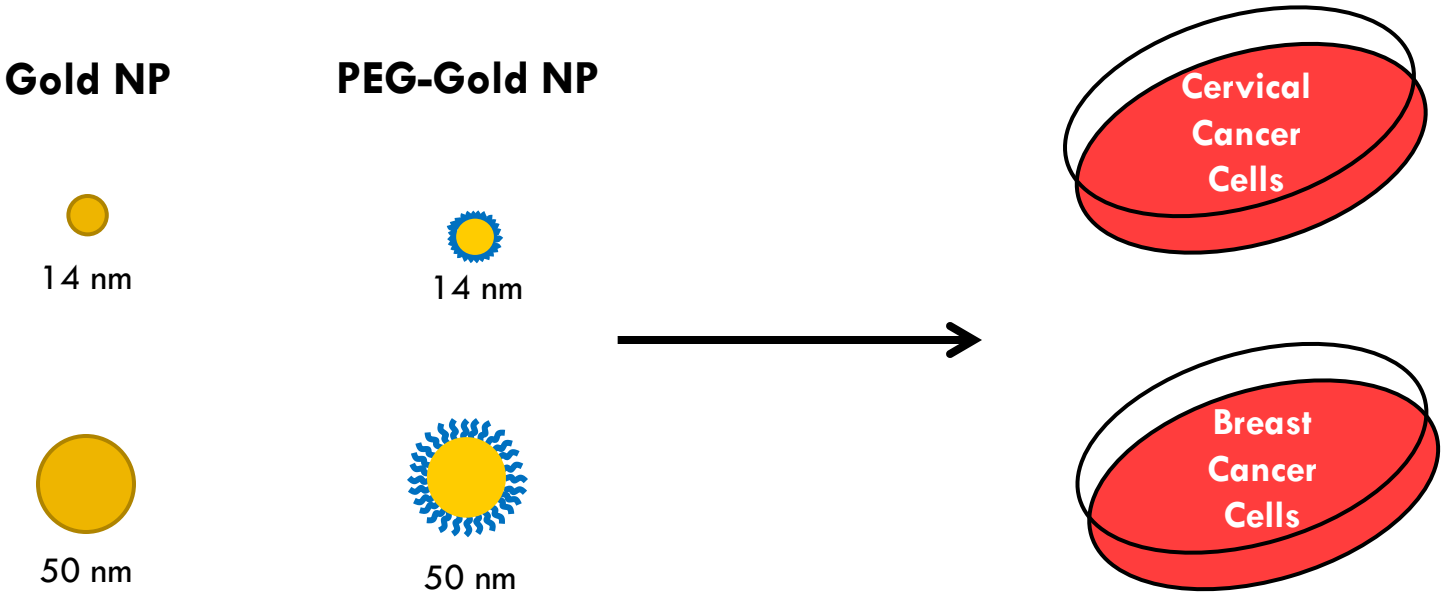
Increases blood circulation time



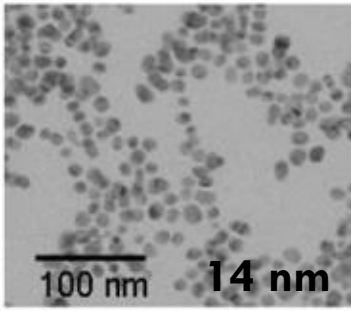
[3]Jokerst JV, Lobovkina T, Zare RN, Gambhir SS. Nanoparticle PEGylation for imaging and therapy. *Nanomedicine (Lond)*. 2011;6(4):715-728.

Objective

- To determine the cellular uptake of gold NPs and PEG-coated ones (2000 Da)



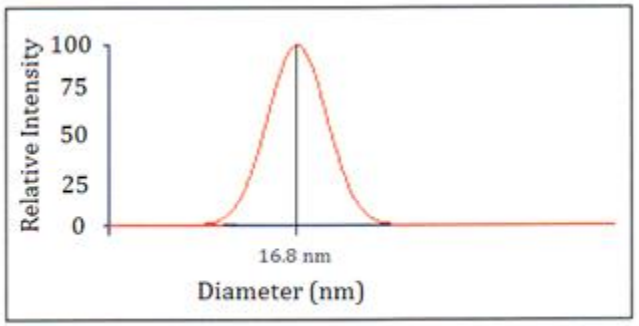
Characterization



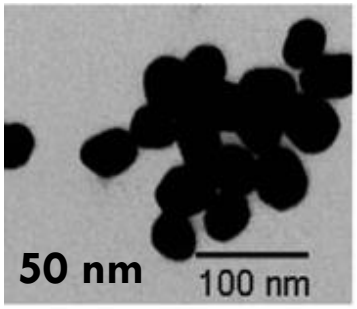
Gold NP

Effective Diameter: 16.8 nm

Polydispersity: 0.176



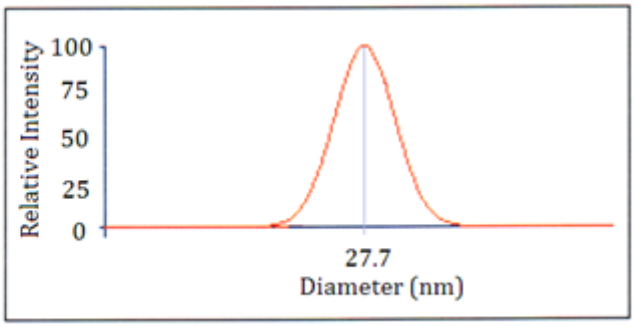
Lognormal Distribution



PEG-Gold NP

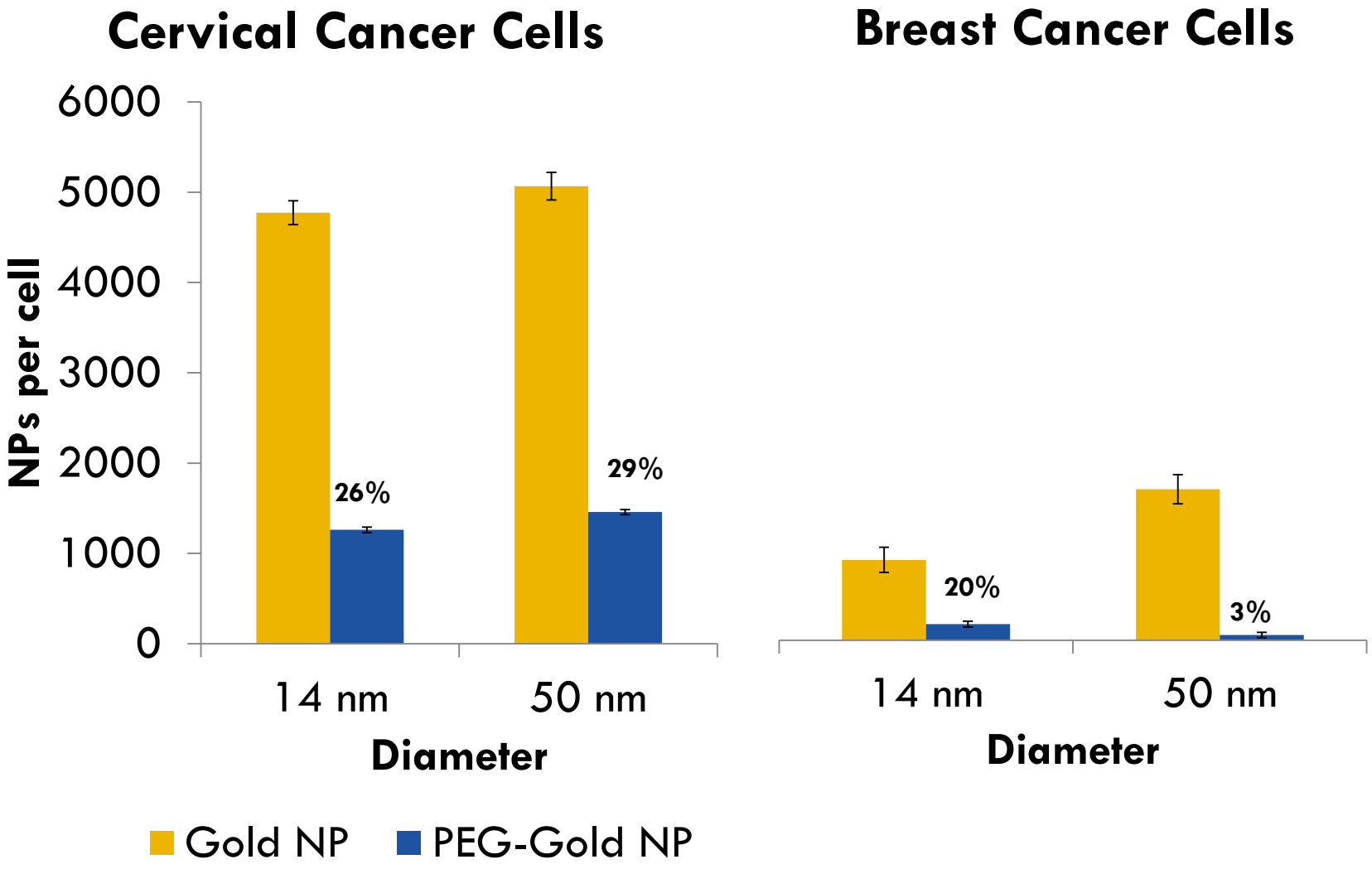
Effective Diameter: 27.7 nm

Polydispersity: 0.071

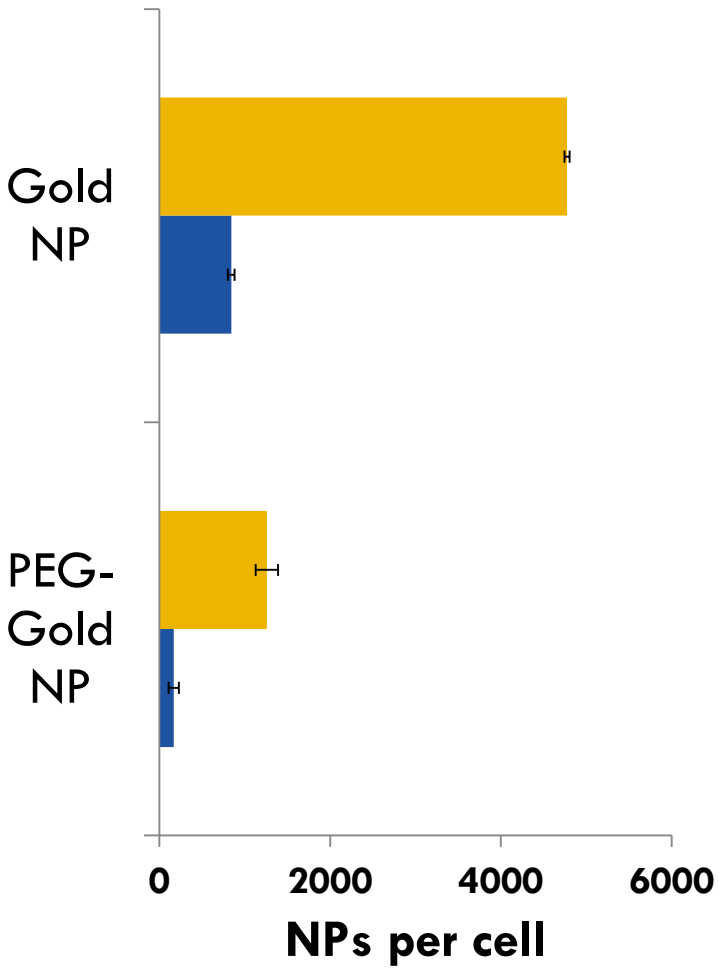


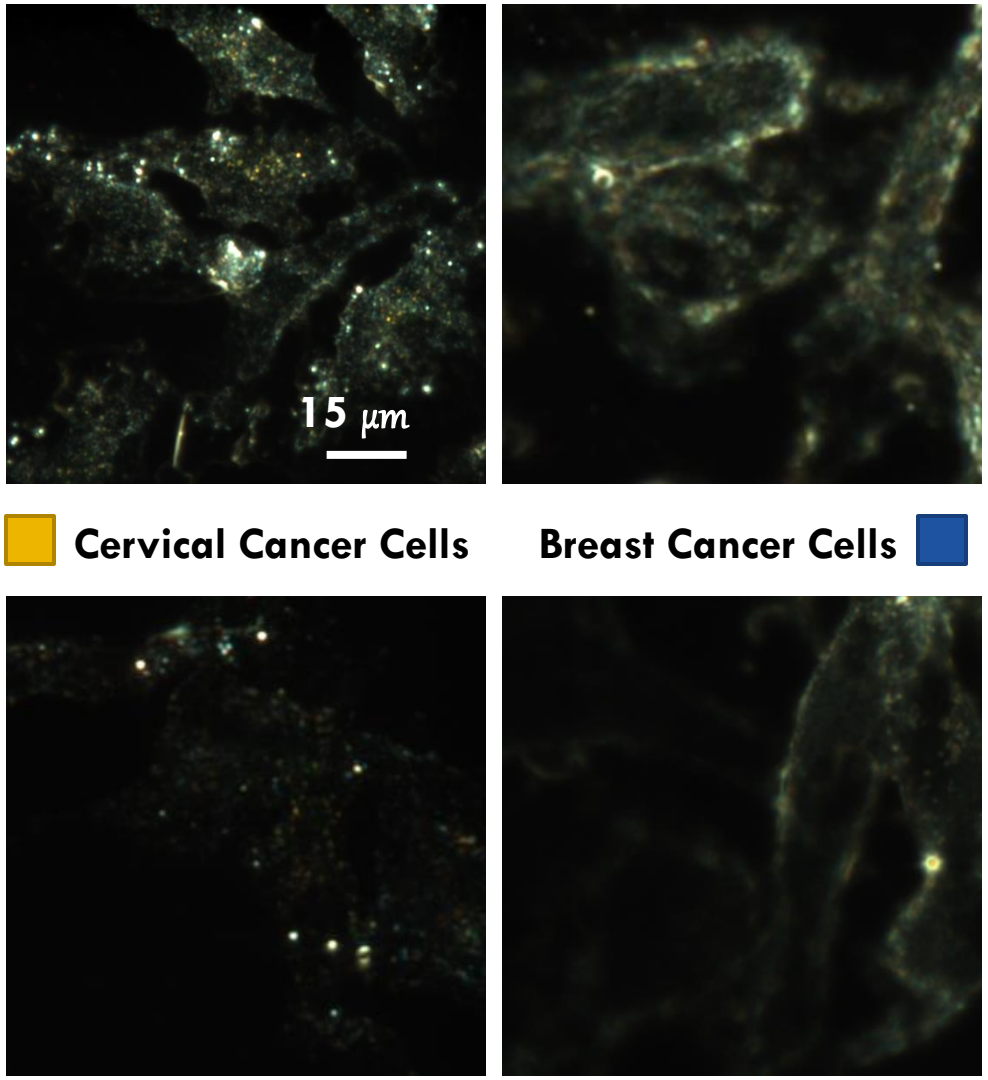
Lognormal Distribution

Cellular uptake results



Darkfield images of 14 nm Gold NPs





Conclusion

- Uptake of PEG-Gold NP is size dependent and cell type dependent.
- In cervical cancer cells, PEG-Gold NP uptake is reduced to 26%.
- In breast cancer cells, PEG-Gold NP uptake is reduced to 20%.
- There is a need to enhance the uptake of PEG-Gold NPs.

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Ding, Y., Zhou, Y. Y., Chen, H., Geng, D. D., Wu, D. Y., Hong, J., et al. (2013). The performance of thiol-terminated PEG-paclitaxel-conjugated gold nanoparticles. *Biomaterials, 34*(38), 10217-10227.

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Liu, Y., Shipton, M. K., Ryan, J., Kaufman, E. D., Franzen, S., & Feldheim, D. L. (2007). Synthesis, stability, and cellular internalization of gold nanoparticles containing mixed peptide-poly(ethylene glycol) monolayers. *Analytical Chemistry, 79*(6), 2221-2229.

Jokerst, J. V., Lobovkina, T., Zare, R. N., & Gambhir, S. S. (2011). Nanoparticle PEGylation for imaging and therapy. *Nanomedicine (London, England), 6*(4), 715-728.

Khlebtsov, N., & Dykman, L. (2011). Biodistribution and toxicity of engineered gold nanoparticles: A review of in vitro and in vivo studies. *Chemical Society Reviews, 40*(3), 1647-1671.

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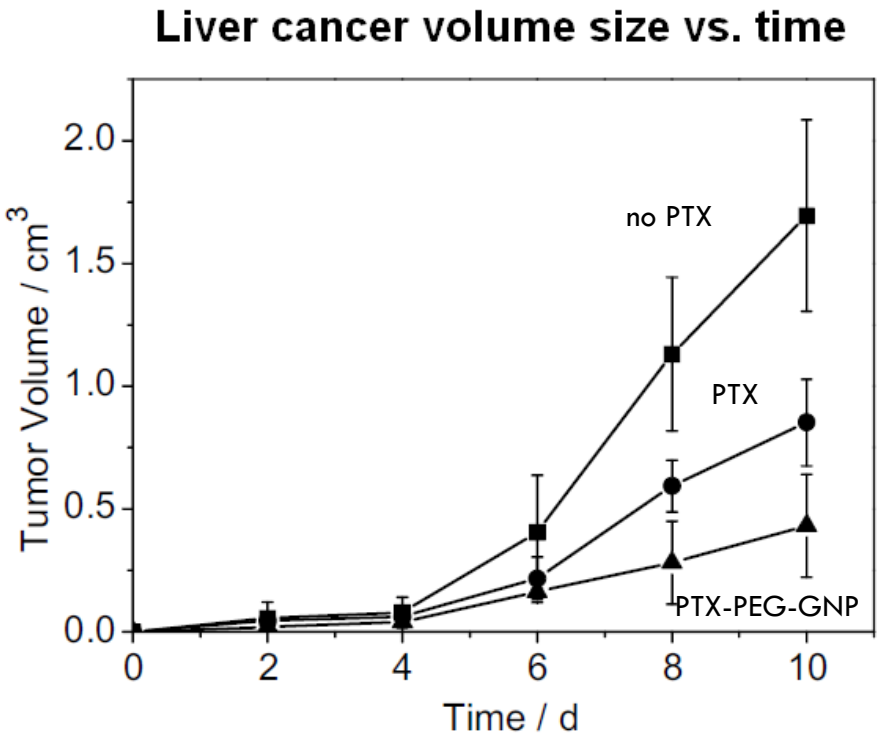
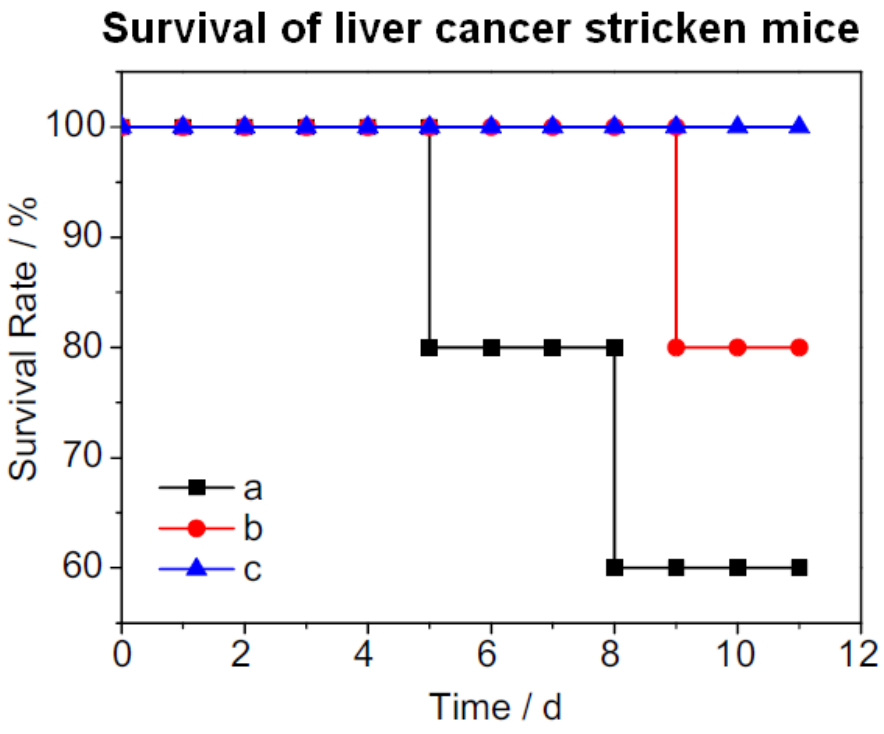
Walkey, C. D., Olsen, J. B., Guo, H., Emili, A., & Chan, W. C. W. (2012). Nanoparticle Size and Surface Chemistry Determine Serum Protein Adsorption and Macrophage Uptake. *J. Am. Chem. Soc., 134* (4), 2139–2147.

Supplementary 1: Drug delivery via PEGylated GNPs

Group a – no PTX, group b – PTX, group c – PTX-PEG-GNPs

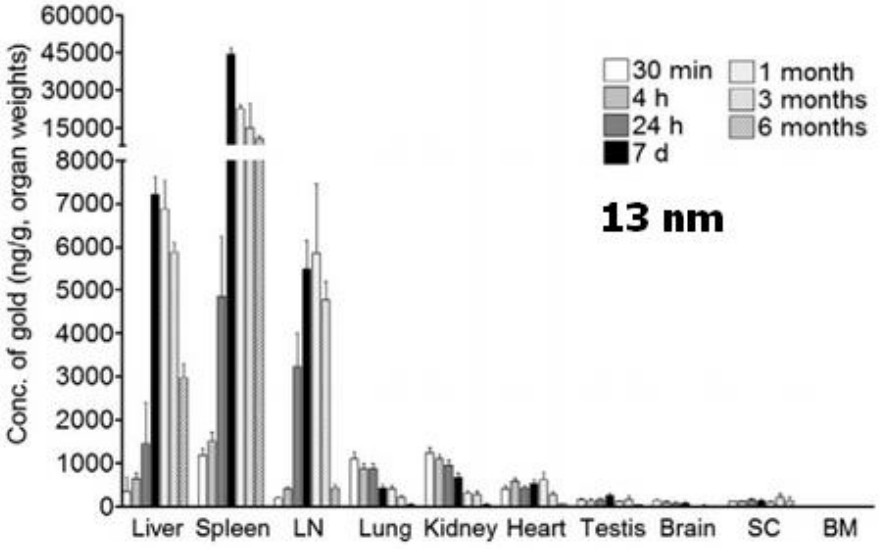


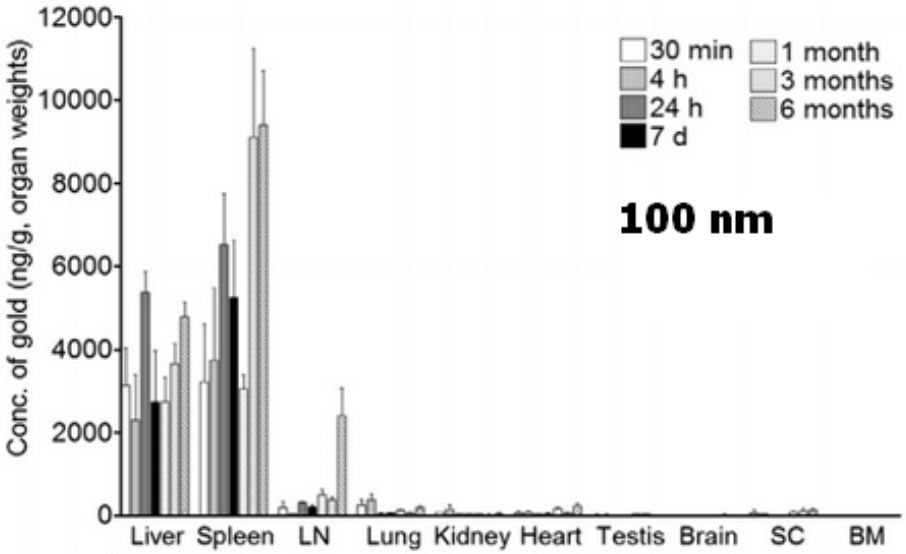


- Lower tumor volume and mass with PEG-GNP conjugation[6]
- Longer drug circulation time of conjugates

[6]Ding Y, Zhou YY, Chen H, et al. The performance of thiol-terminated PEG-paclitaxel-conjugated gold nanoparticles. *Biomaterials*. 2013;34(38):10217-10227.

Supplementary 2: Circulation lifetime depends on GNP size



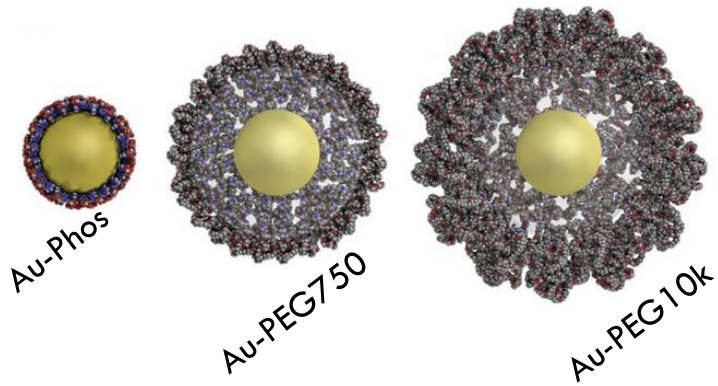


In vivo study by Cho et al[7]

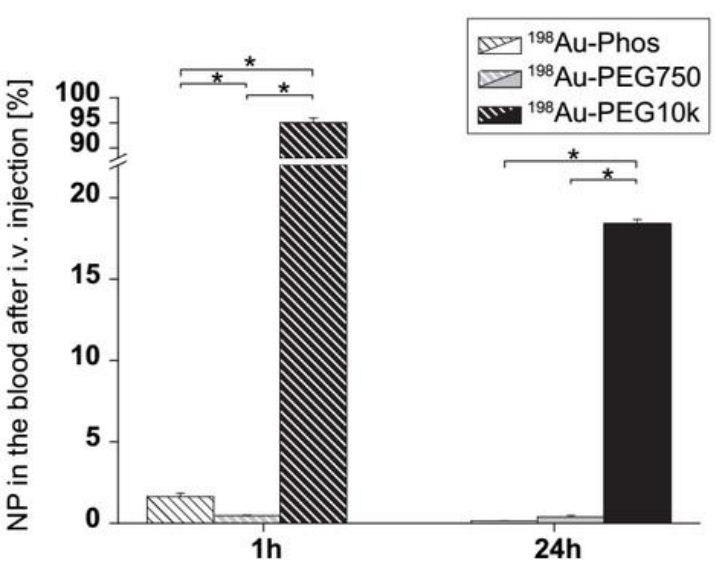
- Varying sizes of GNPs with 2kDa PEG
- Healthy mice
- Larger GNPs had longer circulation lifetimes

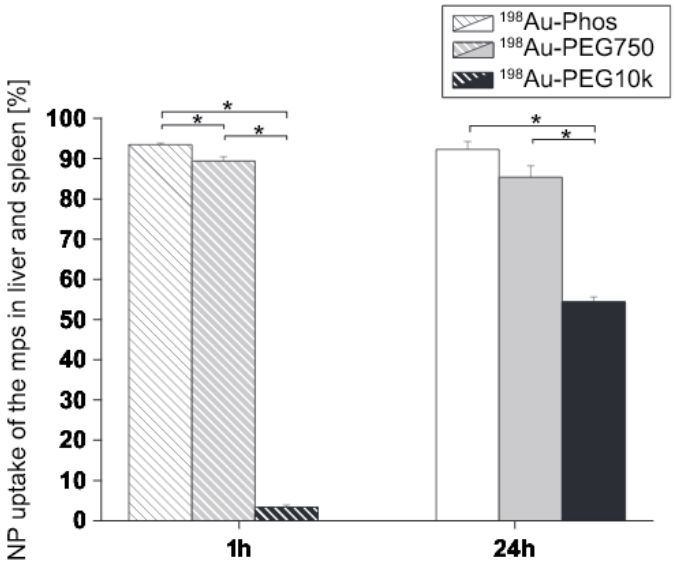
[7]Cho, W. S., Cho, M., Jeong, J., Choi, M., Han, B. S., Shin, H. S., et al. (2010). Size-dependent tissue kinetics of PEG-coated gold nanoparticles. *Toxicology and Applied Pharmacology, 245*(1), 116-123.

Supplementary 3: Circulation lifetime depends on PEG chain length



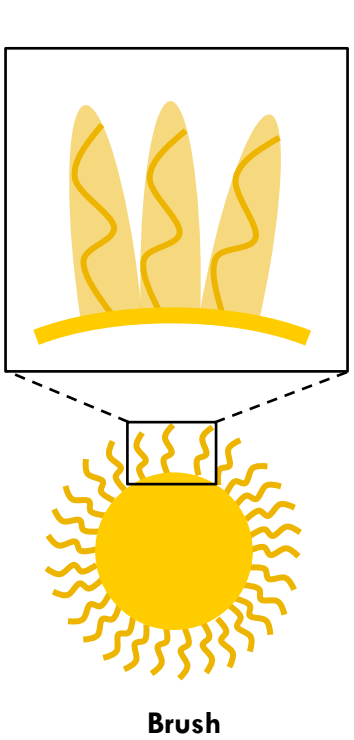
PEGylated 5nm GNPs had longer circulation times with longer PEG chains[8]



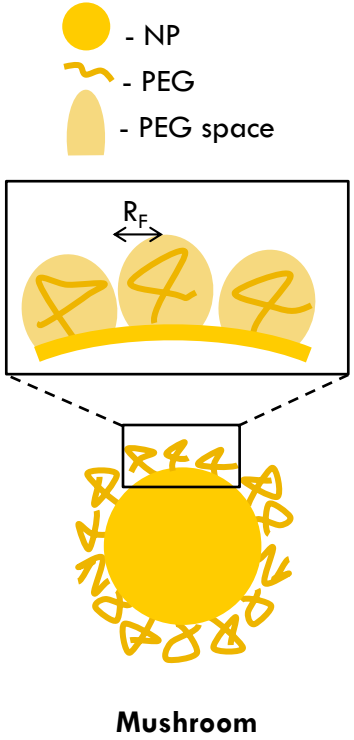


[8]Lipka, J., Semmler-Behnke, M., Sperling, R. A., Wenk, A., Takenaka, S., Schleh, C., et al. (2010). Biodistribution of PEG-modified gold nanoparticles following intratracheal instillation and intravenous injection. *Biomaterials, 31*(25), 6574-6581.

Supplementary 4: Literature Review Queries

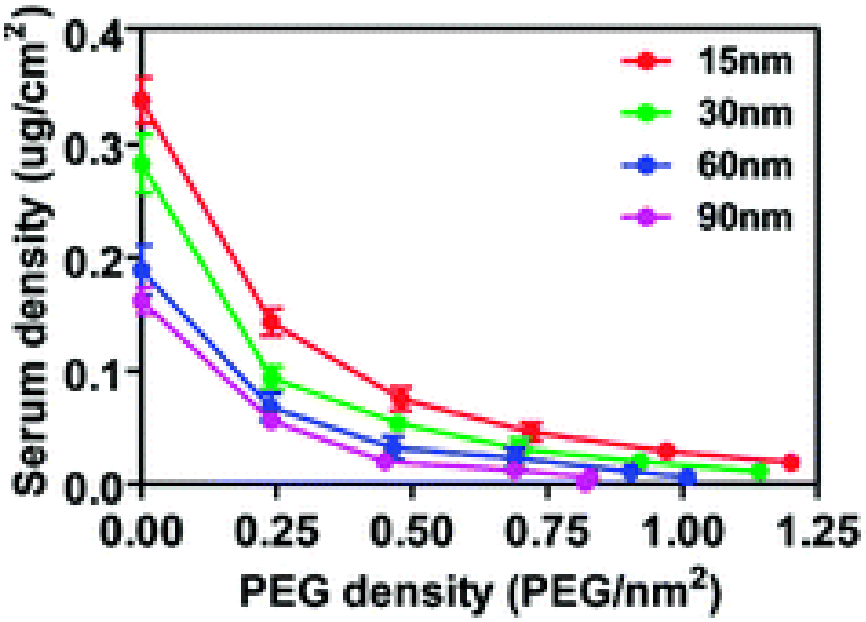


Brush



Mushroom

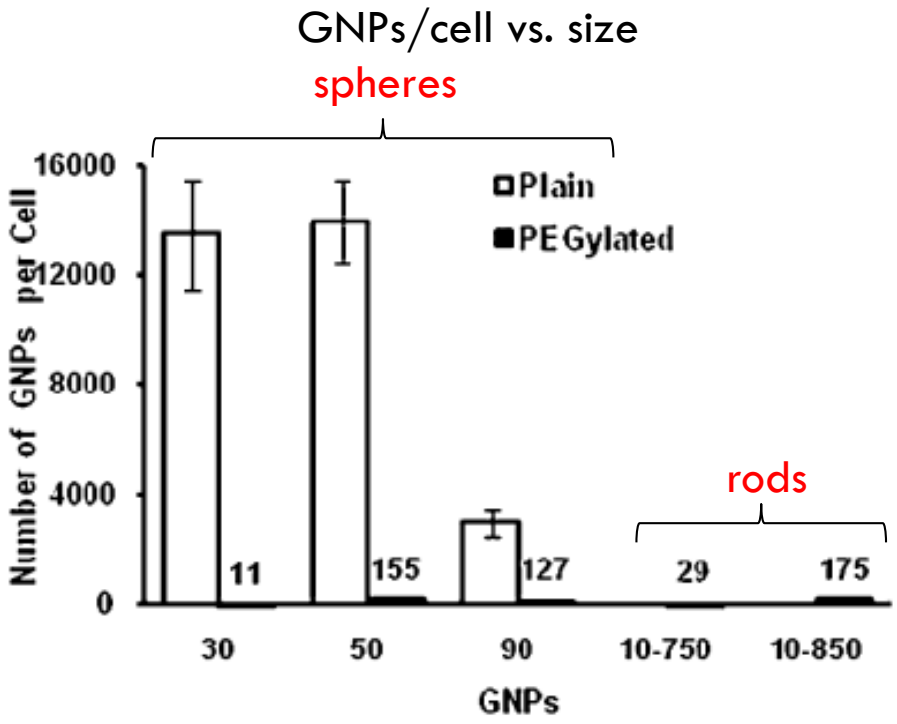
Surface conformation of PEG varied



Surface density of PEG varied[9]

[9]Walkey, C. D., Olsen, J. B., Guo, H., Emili, A., & Chan, W. C. W. (2012). Nanoparticle Size and Surface Chemistry Determine Serum Protein Adsorption and Macrophage Uptake. *J. Am. Chem. Soc.*, *134* (4), 2139–2147.

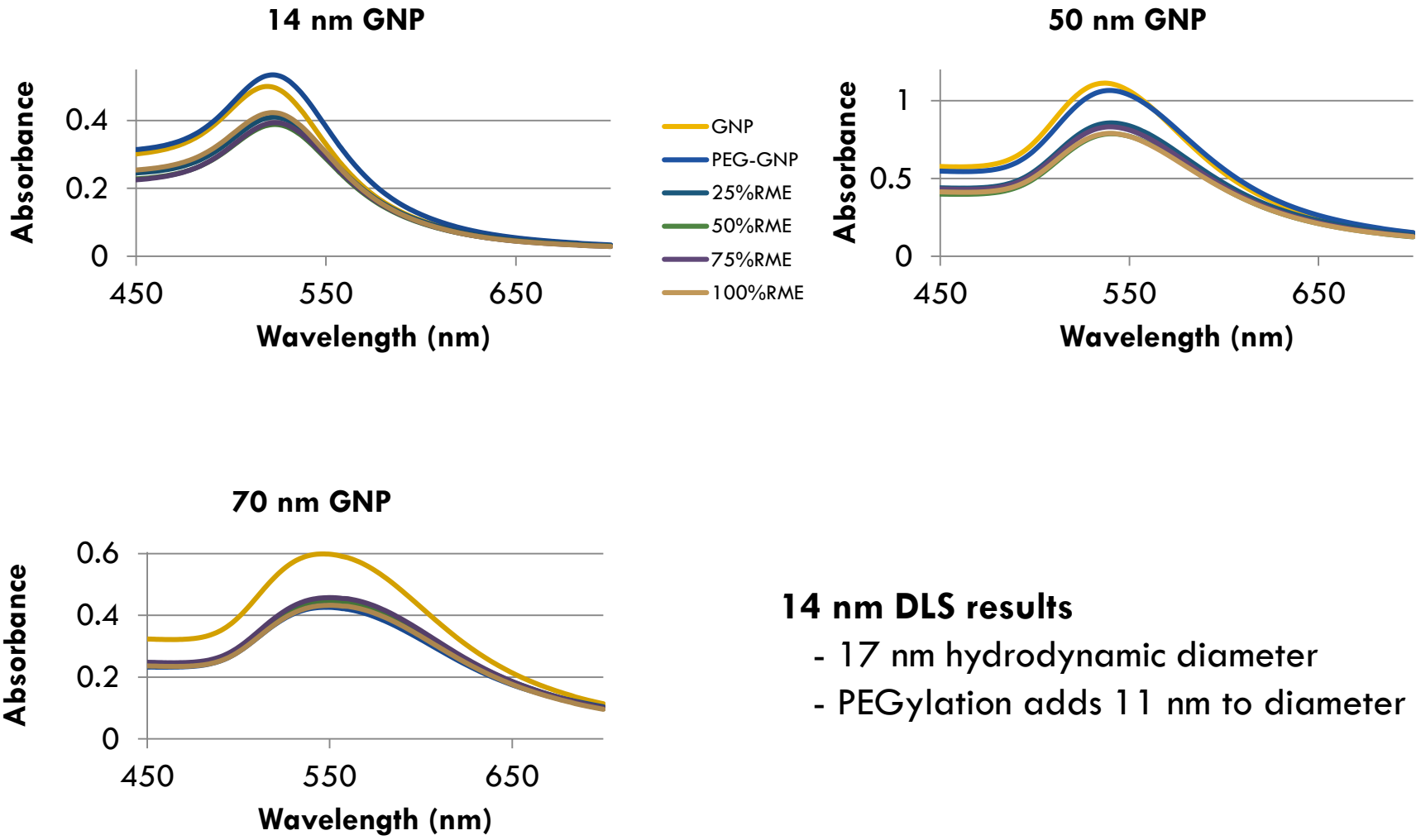
Supplementary 5: From extracellular matrix to cell



- PEGylation of GNPs reduces uptake[10]

[10]Arnida, Malugin, Ghandehari, Cellular uptake and toxicity of gold nanoparticles in prostate cancer cells: a comparative study of rods and spheres,Anal. Chem., 2007, 79, 2221-2229.

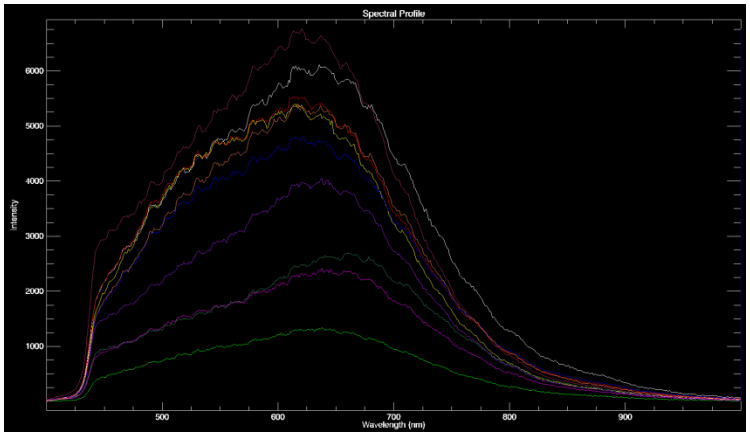
Supplementary 6: Characterization of Conjugates

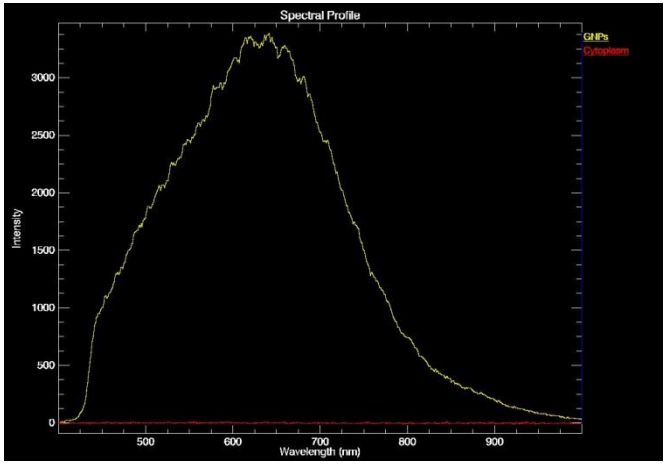


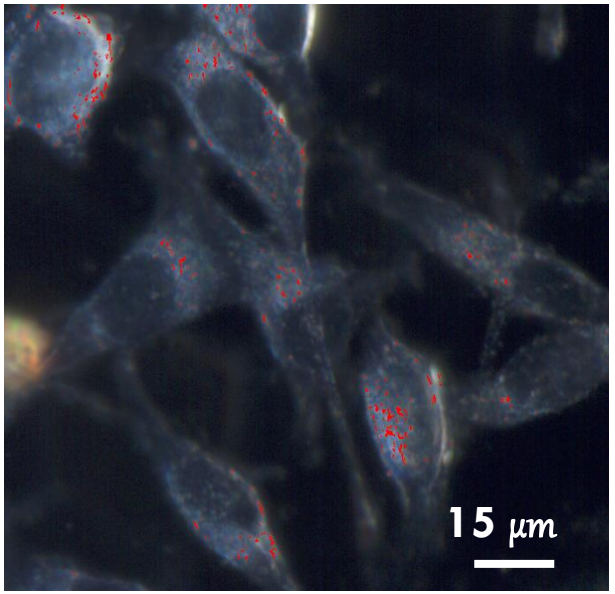
14 nm DLS results

- 17 nm hydrodynamic diameter
- PEGylation adds 11 nm to diameter

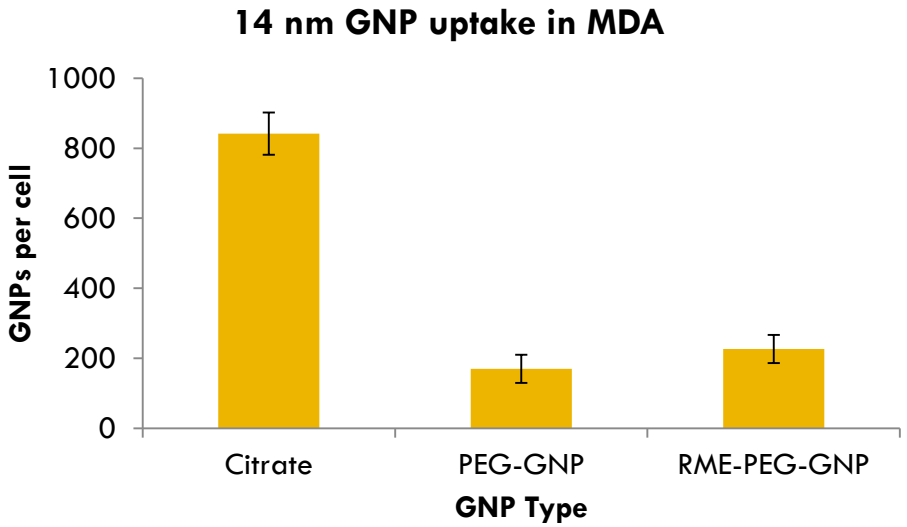
Supplementary 7: HyperSpectral Image for RMEp-PEG-GNPs in MDA cells

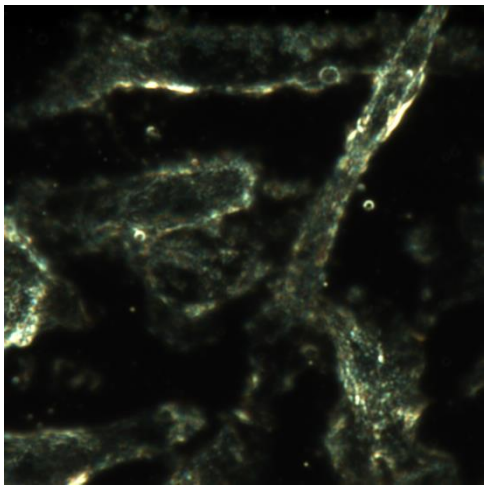


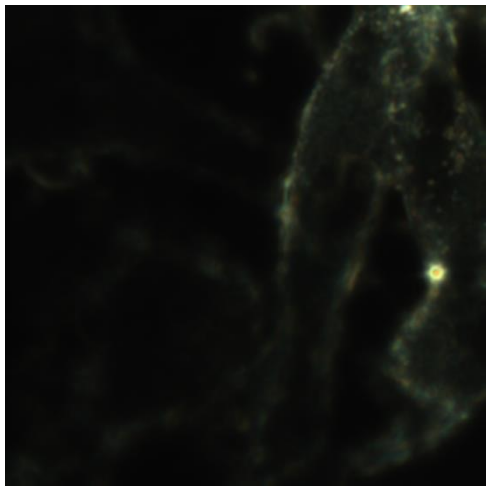


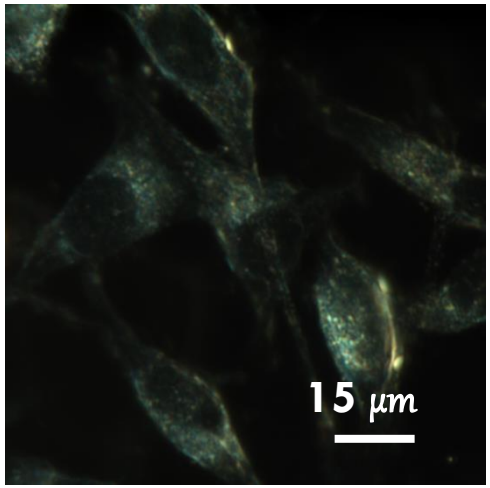


Supplementary 8: Darkfield images of 14 nm gold NPs in MDA









Supplementary 9: Enhanced uptake of 14 nm gold NPs in cervical cancer cells