

- a. Assuming that release of the drug is far from equilibrium, calculate the initial rate of drug release from the particles in units of moles of drug per hour ( $\text{mol h}^{-1}$ ) from the information given.
  - b. If the absorbance of the solution after the system reached equilibrium in 72 hours was 1.163, calculate the ratio of drug remaining in the nanoparticle to that which is free in solution.
- 3 Apoferritin is being considered as a potential delivery vehicle for drugs. Consider a solution which contains the apoferritin monomer,  $2.4 \times 10^{-4} M$ , and a drug,  $30 \text{ mM}$ , which is originally at pH 2.0. When the pH of the solution is raised to 7.4, the individual monomeric subunits associate to form intact apoferritin, which contains 24 subunits in a shell-like structure. If the internal diameter of the apoferritin shell is 8 nm, it is approximately spherical in structure, and there is no active 'recruitment' of drug molecules to the inside of the apoferritin shell when it forms, calculate the approximate average number of drug molecules that would be trapped inside intact apoferritin. The volume of a sphere is  $V = 4/3\pi r^3$ .
  - 4 The longitudinal relaxation rate constant,  $r_1$ , at  $40^\circ\text{C}$ , 60 MHz, of a new  $\text{Ga}^{3+}$  contrast agent was obtained using  $(T_{1(\text{obs})})^{-1} = (T_{1(\text{diam})})^{-1} + r_1[\text{Gd}^{3+}]$ , where  $T_{1(\text{obs})}$  and  $T_{1(\text{diam})}$  are the relaxation time constants of the sample and the matrix in seconds and  $[\text{Gd}^{3+}]$  is the concentration of Gd in mM. Calculate  $T_{1(\text{obs})}$  if  $[\text{Gd}^{3+}] = 0.044 \text{ mM}$ ,  $r_1 = 173 \text{ mM}^{-1} \text{ s}^{-1}$  and  $(T_{1(\text{diam})})^{-1} = 0.25 \text{ s}^{-1}$ .
  - 5 The crystal structure of a gold nanoparticle with bound *p*-mercaptobenzoic acid (*p*-MBA) molecules with the formula  $\text{Au}_{102}(\text{p-MBA})_{44}$  has been published [see Jadzinsky, P.D., Calero, G., Ackerson, C.J., *et al.* (2007) Structure of a thiol monolayer-protected gold nanoparticle at 1.1 Å resolution. *Science*, **318**, 430–433]. The authors of the paper suggested that the reason the cluster is stable is that 44 gold atoms of the cluster contribute their 6s electrons to bonding the 44 *p*-MBA ligands to the cluster, and the remaining 58  $\text{Au}^0$  atoms contribute one electron each to a 'shell,' associated with the entire cluster, that can hold a total of 58 electrons. This accounts for the total of 102, 6s, electrons that are associated with the  $\text{Au}^0$  atoms in the cluster. If 44 Au atoms react with 44 thiols to form 44 two-electron Au–S bonds, write a balanced chemical reaction for what may be taking place when thiols are attached to the gold surface. The electronic configuration of  $\text{Au}^0$  is  $[\text{Xe}]4f^{14}5d^{10}6s^1$ .
  - 6 Calculate the number of gold atoms in a spherical gold nanoparticle with a diameter of 26 nm ( $d = 26 \text{ nm}$ ). The density of gold is  $19.3 \text{ g cm}^{-3}$ .

## References

1. Wang, Y., Zhao, Q., Han, N., *et al.* (2015) Mesoporous silica nanoparticles in drug delivery and biomedical applications. *Nanomed. Nanotech. Biol. Med.*, **11**, 313–327.
2. Baeza, A., Manzano, M., Colilla, M., *et al.* (2016) Recent advances in mesoporous silica nanoparticles for antitumor therapy: our contribution. *Biomater. Sci.*, **4**, 803–813.
3. Lu, F., Doane, T.L., Zhu, J.-J., *et al.* (2012) Gold nanoparticles for diagnostic sensing and therapy. *Inorg. Chim. Acta*, **393**, 142–153.
4. Johnstone, T.C., Suntharalingam, K., and Lippard, S.J. (2016) The next generation of platinum drugs: targeted Pt(II) agents, nanoparticle delivery, and Pt(IV) prodrugs. *Chem. Rev.*, **116**, 3436–3486.
5. Mehra, N.K., Jain, K., and Jain, N.K. (2015) Pharmaceutical and biomedical applications of surface engineered carbon nanotubes. *Drug Disc. Today*, **20**, 750–759.

6. John, A.A., Subramanian, A.P., Vignesh, M., *et al.* (2015) Carbon nanotubes and graphene as emerging candidates in neuroregeneration and neurodrug delivery. *Int. J. Nanomed.*, **10**, 4267–4277.
7. Bhattacharya, K., Mukherjee, S.P., Gallud, A., *et al.* (2016) Biological interactions of carbon-based nanomaterials: From coronation to degradation. *Nanomed. Nanotech. Biol. Med.*, **12**, 333–351.
8. Amstad, E., Textora, M., and Reimhult, E. (2011) Stabilization and functionalization of iron oxide nanoparticles for biomedical applications. *Nanoscale*, **3**, 2819–2843.
9. Liu, H., Zhang, J., Chen, X., *et al.* (2016) Application of iron oxide nanoparticles in glioma imaging and therapy: from bench to bedside. *Nanoscale*, **8**, 7808–7826.
10. Liu, R., Yu, T., Shi, Z., *et al.* (2016) The preparation of metal–organic frameworks and their biomedical application. *Int. J. Nanomed.*, **11**, 1187–1200.
11. Fang, M., Peng, C., Pang, D.-W., *et al.* (2012) Quantum dots for cancer research: current status, remaining issues, and future perspectives. *Cancer Biol. Med.*, **9**, 151–163.
12. Volkov, Y. (2015) Quantum dots in nanomedicine: recent trends, advances and unresolved issues. *Biochem. Biophys. Res. Commun.*, **468**, 419–427.
13. Montalti, M., Prodi, L., Rampazzo, E., *et al.* (2014) Dye-doped silica nanoparticles as luminescent organized systems for nanomedicine. *Chem. Soc. Rev.*, **43**, 4243–4268.
14. Xie, J., Lee, S., and Chen, X. (2010) Nanoparticle-based theranostic agents. *Adv. Drug Deliv. Rev.*, **62**, 1064–1079.
15. Ryu, J.H., Lee, J., Son, S., *et al.* (2014) Theranostic nanoparticles for future personalized medicine. *J. Control. Release*, **190**, 477–484.
16. Lee, B.K., Yun, Y.H., and Park, K. (2015) Smart nanoparticles for drug delivery: boundaries and opportunities. *Chem. Eng. Sci.*, **125**, 158–164.
17. Feliu, N., Docter, D., Heine, M., *et al.* (2016) In vivo degeneration and the fate of inorganic nanoparticles. *Chem. Soc. Rev.*, **45**, 2440–2457.
18. Zhao, F., Zhao, Y., Liu, Y., *et al.* (2011) Cellular uptake, intracellular trafficking, and cytotoxicity of nanomaterials. *Small*, **7**, 1322–1337.
19. Kang, H., Mintri, S., Menon, A.V., *et al.* (2015) Pharmacokinetics, pharmacodynamics and toxicology of theranostic nanoparticles. *Nanoscale*, **7**, 18848–18862.
20. Suk, J.S., Xu, Q., Kim, N., *et al.* (2016) PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. *Adv. Drug Deliv. Rev.*, **99**, 28–51.
21. Alexis, F., Pridgen, E., Molnar, L.K., *et al.* (2008) Factors affecting the clearance and biodistribution of polymeric nanoparticles. *Mol. Pharm.*, **5**, 505–515.
22. Yang, Q., Jones, J.W., Parker, C.L., *et al.* (2014) Evading immune cell uptake and clearance requires PEG grafting at densities substantially exceeding the minimum for brush conformation. *Mol. Pharm.*, **11**, 1250–1258.
23. Pozzi, D., Colapicchioni, V., Caracciolo, G., *et al.* (2014) Effect of polyethyleneglycol (PEG) chain length on the bio–nano-interactions between PEGylated lipid nanoparticles and biological fluids: from nanostructure to uptake in cancer cells. *Nanoscale*, **6**, 2782–2792.
24. Matsumura, Y. and Maeda, H. (1986) A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. *Cancer Res.*, **46**, 6387–6392.
25. Fang, J., Nakamura, H., and Maeda, H. (2011) The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. *Adv. Drug Deliv. Rev.*, **63**, 136–151.
26. Dreaden, E.C., Mackey, M.A., Huang, X., *et al.* (2011) Beating cancer in multiple ways using nanogold. *Chem. Soc. Rev.*, **40**, 3391–3404.
27. Blanco, E., Shen, H., and Ferrari, M. (2015) Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nat. Biotechnol.*, **33**, 941–951.
28. Kwon, I.K., Lee, S.C., Han, B., *et al.* (2012) Analysis on the current status of targeted drug delivery to tumors. *J. Control. Release*, **164**, 108–114.
29. Sano, K., Nakajima, T., Choyke, P.L., *et al.* (2013) Markedly enhanced permeability and retention effects induced by photo-immunotherapy of tumors. *ACS Nano*, **7**, 717–724.
30. Mitsunaga, M., Ogawa, M., Kosaka, N., *et al.* (2011) Cancer cell-selective *in vivo* near-infrared photoimmunotherapy targeting specific membrane molecules. *Nat. Med.*, **17**, 1685–1692.

31. Yu, M.K., Park, J., and Jon, S. (2012) Targeting strategies for multifunctional nanoparticles in cancer imaging and therapy. *Theranostics*, **2**, 3–44.
32. Danhier, F., Le Breton, A., and Préat, V. (2012) RGD-based strategies to target alpha(v) beta(3) integrin in cancer therapy and diagnosis. *Mol. Pharm.*, **9**, 2961–2973.
33. Alexander, C.M., Hamner, K.L., Maye, M.M., and Dabrowiak, J.C. (2014) Multifunctional DNA-gold nanoparticles for targeted doxorubicin delivery. *Bioconjug. Chem.*, **25**, 1261–1271.
34. Xu, S., Olenyuk, B.Z., Okamoto, C.T., *et al.* (2013) Targeting receptor-mediated endocytotic pathways with nanoparticles: rationale and advances. *Adv. Drug Deliv. Rev.*, **65**, 121–138.
35. Kettiger, H., Schipanski, A., Wick, P., *et al.* (2013) Engineered nanomaterial uptake and tissue distribution: from cell to organism. *Int. J. Nanomed.*, **8**, 3255–3269.
36. Wang, P., Wang, X., Wang, L., *et al.* (2015) Interaction of gold nanoparticles with proteins and cells. *Sci. Technol. Adv. Mater.* **16**, 034610 (15pp).
37. Mijndonckx, K., Leys, N., Mahillon, J., *et al.* (2013) Antimicrobial silver: uses, toxicity and potential for resistance. *Biometals*, **26**, 609–621.
38. Caballero-Díaz, E., Pfeiffer, C., Kastl, L., *et al.* (2013) The toxicity of silver nanoparticles depends on their uptake by cells and thus on their surface chemistry. *Part. Part. Syst. Char.*, **30**, 1079–1085.
39. Papasani, M.R., Wang, G., and Hill, R.A. (2012) Gold nanoparticles: the importance of physiological principles to devise strategies for targeted drug delivery. *Nanomed. Nanotech. Biol. Med.*, **8**, 804–814.
40. Yang, C., Yohana, D., and Chithrani, D.B. (2014) Optimized bio-nano interface using peptide modified colloidal gold nanoparticles. *J. Colloid Interface Sci. Commun.*, **1**, 54–56.
41. Guo, S. and Huang, L. (2011) Nanoparticles escaping RES and endosome: Challenges for siRNA delivery for cancer therapy. *J. Nanomater.*, doi:10.1155/2011/742895.
42. Kreyling, W.G., Abdelmonem, A.M., Ali, Z., *et al.* (2015) In vivo integrity of polymer-coated gold nanoparticles. *Nat. Nanotechnol.*, **10**, 619–623.
43. Andón, F.T., Kapralov, A.A., Yanamala, N., *et al.* (2013) Biodegradation of single-walled carbon nanotubes by eosinophil peroxidase. *Small*, **9**, 2721–2729.
44. Kagan, V.E., Konduru, N.V., Feng, W., *et al.* (2010) Carbon nanotubes degraded by neutrophil myeloperoxidase induce less pulmonary inflammation. *Nat. Nanotechnol.*, **5**, 354–359.
45. Arami, H., Khandhar, A., Liggitt, D., *et al.* (2015) In vivo delivery, pharmacokinetics, biodistribution and toxicity of iron oxide nanoparticles. *Chem. Soc. Rev.*, **44**, 8576–8607.
46. Lévy, M., Luciani, N., Alloeyau, D., *et al.* (2011) Long-term in-vivo biotransformation of iron oxide nanoparticles. *Biomaterials*, **32**, 3988–3999.
47. Lévy, M., Lagarde, F., and Maraloiu, V.-A. (2010) Degradability of superparamagnetic nanoparticles in a model of intracellular environment: follow-up of magnetic, structural and chemical properties. *Nanotechnology*, **21**, doi:10.1088/0957-4484/21/39/395103
48. Li, L., Jiang, W., Luo, K., *et al.* (2011) Superparamagnetic iron oxide nanoparticles as MRI contrast agents for non-invasive stem cell labeling and tracking. *Theranostics*, **3**, 595–615.
49. Wang, Y.J. (2011) Superparamagnetic iron oxide-based MRI contrast agents: Current status of clinical application. *Quant. Imaging Med. Surg.*, **1**, 35–40.
50. Zhai, W., He, C., Wu, L., *et al.* (2012) Degradation of hollow mesoporous silica nanoparticles in human umbilical vein endothelial cells. *J. Biomed. Mater. Res. Part B*, **100B**, 1397–1403.
51. Corazzari, I., Gilardino, A., Dalmazzo, A., *et al.* (2013) Localization of CdSe/ZnS quantum dots in the lysosomal acidic compartment of cultured neurons and its impact on viability: Potential role of ion release. *Toxicol. In Vitro*, **27**, 752–759.
52. Pathakoti, K., Hwang, H.-M., Xu, H., *et al.* (2013) In vitro cytotoxicity of CdSe/ZnS quantum dots with different surface coatings to human keratinocytes HaCaT cells. *J. Environ. Sci.*, **25**, 163–171.
53. Cai, W., Chu, C.C., and Liu, G. (2015) Metal–organic framework-base nanomedicine platforms for drug delivery and molecular imaging. *Small*, **11**, 4806–4822.
54. Rijnaarts, T., Mejia-Ariza, R., Egberink, R.J.M., *et al.* (2015) Metal–organic frameworks (MOFs) as multivalent materials: size control and surface functionalization by monovalent capping ligands. *Chem. Eur. J.*, **21**, 10296–10301.
55. Baati, T., Njim, L., Neffati, F., *et al.* (2013) In-depth analysis of the in vivo toxicity of nanoparticles of porous iron(III) metal–organic frameworks. *Chem. Sci.*, **4**, 1597–1607.

56. He, C., Lu, K., Liu, D., *et al.* (2014) Nanoscale metal–organic frameworks for the co-delivery of cisplatin and pooled siRNAs to enhance therapeutic efficacy in drug-resistant ovarian cancer cells. *J. Am. Chem. Soc.*, **136**, 5181–5184.
57. Longmire, M., Choyke, P.L., and Kobayashi, H. (2008) Clearance properties of nano-sized particles and molecules as imaging agents: considerations and caveats. *Nanomedicine (Lond.)*, **3**, 703–717.
58. Toy, R., Peiris, P.M., Ghaghada, K.B., *et al.* (2014) Shaping cancer nanomedicine: The effect of particle shape on the *in vivo* journey of nanoparticles. *Nanomedicine (Lond.)*, **9**, 121–134.
59. <https://en.wikipedia.org/wiki/Nanomedicine> (accessed May 2016).
60. Liu, G., Men, P., Kudo, W., *et al.* (2009) Nanoparticle-chelator conjugates as inhibitors of amyloid- $\beta$  aggregation and neurotoxicity: a novel therapeutic approach for Alzheimer disease. *Neurosci. Lett.*, **455**, 187–190.
61. Gregori, M., Masserini, M., and Mancini, S. (2015) Nanomedicine for the treatment of Alzheimer's disease. *Nanomedicine (Lond.)*, **10**, 1203–1218.
62. Lauzon, M.-A., Daviau, A., Marcos, B., *et al.* (2015) Nanoparticle-mediated growth factor delivery systems: A new way to treat Alzheimer's disease. *J. Control. Release*, **206**, 187–205.
63. Lee, S.-M., Kim, H. J., Ha, Y.-J., *et al.* (2013) Targeted chemo-photothermal treatments of rheumatoid arthritis using gold half-shell multifunctional nanoparticles. *ACS Nano*, **7**, 50–57.
64. Marradi, M., Di Gianvincenzo, P., Enríquez-Navas, P.M., *et al.* (2011) Gold nanoparticles coated with oligomannosides of HIV-1 glycoprotein gp120 mimic the carbohydrate epitope of antibody 2G12. *J. Mol. Biol.*, **410**, 798–810.
65. Koneru, B., Shi, Y., Wang, Y.-C., *et al.* (2015) Tetracycline-containing MCM-41 mesoporous silica nanoparticles for the treatment of *Escherichia coli*. *Molecules*, **20**, 19690–19698.
66. Rizzello, L. and Pompa, P.P. (2014) Nanosilver-based antibacterial drugs and devices: Mechanisms, methodological drawbacks, and guidelines. *Chem. Soc. Rev.*, **43**, 1501–1518.
67. Duncan, B., Li, X., Landis, R.F., *et al.* (2015) Nanoparticle-stabilized capsules for the treatment of bacterial biofilms. *ACS Nano*, **9**, 7775–7782.
68. Black, K.C.L., Wang, Y., Luehmann, H.P., *et al.* (2014) Radioactive  $^{198}\text{Au}$ -doped nanostructures with different shapes for *in vivo* analyses of their biodistribution, tumor uptake, and intratumoral distribution. *ACS Nano*, **8**, 4385–4394.
69. Turkevich, J., Stevenson, P.C., and Hillier, J. (1951) A Study of the nucleation and growth processes in the synthesis of colloidal gold. *Discuss. Faraday Soc.*, **11**, 55–75.
70. Li, C., Li, D., Wan, G., *et al.* (2011) Facile synthesis of concentrated gold nanoparticles with low size-distribution in water: temperature and pH controls. *Nanoscale Res. Lett.*, **6**, 440.
71. Libutti, S.K., Paciotti, G.F., Byrnes, A.A., *et al.* (2010) Phase I and pharmacokinetic studies of CYT-6091, a novel PEGylated colloidal gold-rhTNF nanomedicine. *Clin. Cancer Res.*, **16**, 6139–6149.
72. Paciotti, G.F., Kingston, D.G.I., and Tamarkin, L. (2006) Colloidal gold nanoparticles: a novel nanoparticle platform for developing multifunctional tumor-targeted drug delivery vectors. *Drug Dev. Res.*, **67**, 47–54.
73. Paciotti, G.F., Myer, L., Weinreich, D., *et al.* (2004) Colloidal gold: a novel nanoparticle vector for tumor-directed drug delivery. *Drug Deliv.*, **11**, 169–183.
74. <https://clinicaltrials.gov> (accessed May 2016).
75. Jain, S., Hirst, D.G., and O'Sullivan, J.M. (2012) Gold nanoparticles as novel agents for cancer therapy. *Br. J. Radiol.*, **85**, 101–113.
76. van Horssen, R., ten Hagen, T.L.M., and Eggermont, A.M.M. (2006) TNF- $\alpha$  in cancer treatment: molecular insights, antitumor effects, and clinical utility. *Oncologist*, **11**, 397–408.
77. Huang, X., Jain, P.K., El-Sayed, I.H., *et al.* (2008) Plasmonic photothermal therapy (PPTT) using gold nanoparticles. *Lasers Med. Sci.*, **23**, 217–228.
78. Dreaden, E.C. and El-Sayed, M.A. (2012) Detecting and destroying cancer cells in more than one way with noble metals and different confinement properties on the nanoscale. *Acc. Chem. Res.*, **45**, 1854–1865.
79. Austin, L.A., Mackey, M.A., Dreaden, E.C., *et al.* (2014) The optical, photothermal, and facile surface chemical properties of gold and silver nanoparticles in biodiagnostics, therapy and drug delivery. *Arch. Toxicol.*, **88**, 1391–1417.
80. Lim, J., Yeap, S.P., Che, H.X., *et al.* (2013) Characterization of magnetic nanoparticle by dynamic light scattering. *Nanoscale Res. Lett.*, **8**, 381

81. Zhang, Y., Yang, M., and Portney, N.P. (2008) Zeta potential: a surface electrical characteristic to probe the interaction of nanoparticles with normal and cancer human breast epithelial cells. *Biomed. Microdevices*, **10**, 321–328.
82. Hone, D.C., Walker, P.I., Evans-Gowing, R., *et al.* (2002) Generation of cytotoxic singlet oxygen via phthalocyanine-stabilized gold nanoparticles: a potential delivery vehicle for photodynamic therapy. *Langmuir*, **18**, 2985–2987.
83. <https://clinicaltrials.gov/ct2/show/NCT01800838> (accessed May 2016).
84. Cheng, Y., Samia, A.C., Meyers, J.D., *et al.* (2008) Highly efficient drug delivery with gold nanoparticle vectors for *in vivo* photodynamic therapy of cancer. *J. Am. Chem. Soc.*, **130**, 10643–10647.
85. Cheng, Y., Doane, T.L., Chuang, C.-H., *et al.* (2014) Near infrared light-triggered drug generation and release from gold nanoparticle carriers for photodynamic therapy. *Small*, **10**, 1799–1804.
86. Ghosh, P., Han, G., De, M., *et al.* (2008) Gold nanoparticles in delivery applications. *Adv. Drug Deliv. Rev.*, **60**, 1307–1315.
87. Craig, G.E., Brown, S.D., Lamprou, D.A., *et al.* (2012) Cisplatin-tethered gold nanoparticles that exhibit enhanced reproducibility, drug loading, and stability: a step closer to pharmaceutical approval? *Inorg. Chem.*, **51**, 3490–3497.
88. Shi, Y., Goodisman, J., and Dabrowiak, J.C. (2013) Cyclodextrin-capped gold nanoparticles as a delivery vehicle for a prodrug of cisplatin. *Inorg. Chem.*, **52**, 9418–9426.
89. Pathak, R.K., McNitt, C.D., Popik, V.V., *et al.* (2014) A versatile bioorthogonal copper-free click chemistry platform to functionalize cisplatin prodrugs. *Chemistry*, **20**, 6861–6865.
90. Kresge, C.T., Leonowicz, M.E., Roth, W.J., *et al.* (1992) Ordered mesoporous molecular sieves synthesized by a liquid-crystal template mechanism. *Nature*, **359**, 710–712.
91. Munaweera, I., Shi, Y., Koneru, B., *et al.* (2015) Nitric oxide- and cisplatin-releasing silica nanoparticles for use against non-small cell lung cancer. *J. Inorg. Biochem.*, **153**, 23–31.
92. Tao, Z., Xie, Y., Goodisman, J., *et al.* (2010) Isomer-dependent adsorption and release of *cis*- and *trans*-platin anticancer drugs by mesoporous silica nanoparticles. *Langmuir*, **26**, 8914–8924.
93. Yang, P., Gai, S., and Lin, J. (2012) Functionalized mesoporous silica materials for controlled drug delivery. *Chem. Soc. Rev.*, **41**, 3679–3698.
94. Li, Z., Barnes, J.C., Bosoy, A., *et al.* (2012) Mesoporous silica nanoparticles in biomedical applications. *Chem. Soc. Rev.*, **41**, 2590–2605.
95. Slowing, I.I., Vivero-Escoto, J.L., Wu, C.-W., *et al.* (2008) Mesoporous silica nanoparticles as controlled release drug delivery and gene transfection carriers. *Adv. Drug Deliv. Rev.*, **60**, 1278–1288.
96. Mamaeva, V., Sahlgren, C., and Lindén, M. (2013) Mesoporous silica nanoparticles in medicine – Recent advances. *Adv. Drug Deliv. Rev.*, **65**, 689–702.
97. Baeza, A., Colilla, M., and Vallet-Regí, M. (2015) Advances in mesoporous silica nanoparticles for targeted stimuli-responsive drug delivery. *Expert Opin. Drug Deliv.*, **12**, 319–337.
98. Yang, K.-N., Zhang, C.-Q., Wang, W., *et al.* (2014) pH-responsive mesoporous silica nanoparticles employed in controlled drug delivery systems for cancer treatment. *Cancer Biol. Med.*, **11**, 34–43.
99. Meng, H., Xue, M., Xia, T., *et al.* (2010) Autonomous *in vitro* anticancer drug release from mesoporous silica nanoparticles by pH-sensitive nanovalves. *J. Am. Chem. Soc.*, **132**, 12690–12697.
100. Rocca, J.D., Liu, D., and Lin, W. (2011) Nanoscale metal-organic frameworks for biomedical imaging and drug delivery. *Acc. Chem. Res.*, **44**, 957–968.
101. Horcajada, P., Chalati, T., Serre, C., *et al.* (2010) Porous metal-organic-framework nanoscale carriers as a potential platform for drug delivery and imaging. *Nat. Mater.*, **9**, 172–178.
102. Sun, C.-Y., Qin, C., Wang, X.-L., *et al.* (2013) Metal-organic frameworks as potential drug delivery systems. *Expert Opin. Drug Deliv.*, **10**, 89–101.
103. Horcajada, P., Serre, C., Vallet-Regí, M., *et al.* (2006) Metal-organic frameworks as efficient materials for drug delivery. *Angew. Chem. Int. Ed.* **45**, 5974–5978.
104. Rieter, W.J., Pott, K.M., Taylor, K.M.L., *et al.* (2008) Nanoscale coordination polymers for platinum-based anticancer drug delivery. *J. Am. Chem. Soc.*, **130**, 11584–11585.
105. Estelrich, J., Sánchez-Martín, M.J., and Busquets, M.A. (2015) Nanoparticles in magnetic resonance imaging: from simple to dual contrast agents. *Int. J. Nanomed.*, **10**, 1727–1741.

106. Wang, Y.J. (2011) Superparamagnetic iron oxide-based MRI contrast agents: Current status of clinical application. *Quant. Imaging Med. Surg.* **1**, 35–40.
107. Shin, T.-H., Choi, Y., Kim, S., *et al.* (2015) Recent advances in magnetic nanoparticle-based multi-modal imaging. *Chem. Soc. Rev.*, **44**, 4501–4516.
108. Burtea, C., Laurent, S., Vander, E.L., and Muller, R.N. (2008) Contrast agents: Magnetic resonance. *Handb. Exp. Pharmacol.*, **185** (Pt 1), 135–165.
109. Krause, W. (2002) Contrast agents I. Magnetic resonance imaging, in *Topics in Current Chemistry*, vol. **221**, Ch. 6, pp. 165–199, Springer, Berlin, Germany.
110. Kim, T., Murakami, T., Hori, M., *et al.* (2009) Effect of superparamagnetic iron oxide on tumor-to-liver contrast at T2\*-weighted gradient-echo MRI: Comparison between 3.0 T and 1.5 T MR systems. *J. Magn. Reson. Imaging*, **29**, 595–600.
111. Bae, K.-H., Kim, Y.B., Lee, Y., *et al.* (2010) Bioinspired synthesis and characterization of gadolinium-labeled magnetite nanoparticles for dual contrast T1- and T2-weighted magnetic resonance imaging. *Bioconj. Chem.*, **21**, 505–512.
112. Zhou, Z., Huang, D., Bao, J., *et al.* (2012) A synergistically enhanced T1–T2 dual-modal contrast agent. *Adv. Mater.*, **24**, 6223–6228.
113. Lee, H., Yu, M.K., Park, S., *et al.* (2007) Thermally cross-linked superparamagnetic iron oxide nanoparticles: synthesis and application as a dual imaging probe for cancer in vivo. *J. Am. Chem. Soc.*, **129**, 12739–12745.
114. Hsiao, J.-K., Tsai, C.-P., Chung, T.-H., *et al.* (2008) Mesoporous silica nanoparticles as a delivery system of gadolinium for effective human stem cell tracking. *Small*, **4**, 1445–1452.
115. Lu, X., Feng, L., Akasaka, T., *et al.* (2012) Current status and future developments of endohedral metallofullerenes. *Chem. Soc. Rev.*, **41**, 7723–7760.
116. <https://clinicaltrials.gov/ct2/show/NCT02106598>. <https://clinicaltrials.gov/ct2/results?term=NCT01266096&Search=Search> (accessed May 2016).
117. Phillips, E., Penate-Medina, O., and Zanzonico, P.B. (2014) Clinical translation of an ultrasmall inorganic optical-PET imaging nanoparticle probe. *Sci. Transl. Med.*, **6**, pp. 260ra149.
118. Benezra, M., Penate-Medina, O., and Zanzonico, P.B. (2011) Multimodal silica nanoparticles are effective cancer-targeted probes in a model of human melanoma. *J. Clin. Invest.*, **121**, 2768–2780.
119. Wegner, D.K. and Hildebrandt, N. (2015) Quantum dots: bright and versatile in vitro and in vivo fluorescence imaging biosensors. *Chem. Soc. Rev.*, **44**, 4792–4834.
120. Algar, W.R., Susumu, K., Delehanty, J.B., *et al.* (2011) Semiconductor quantum dots in bioanalysis: crossing the Valley of Death. *Anal. Chem.*, **83**, 8826–8837.
121. Bailey, R.E., Smith, A.M., and Nie, S. (2004) Quantum dots in biology and medicine. *Physica E*, **25**, 1–12.
122. Li, H., Dou, S.-X., Liu, Y.-R., *et al.* (2015) Mapping intracellular diffusion distribution using single quantum dot tracking: compartmentalized diffusion defined by endoplasmic reticulum. *J. Am. Chem. Soc.*, **137**, 436–444.
123. Lim, E.-K., Kim, T., Paik, S., *et al.* (2015) Nanomaterials for theranostics: recent advances and future challenges. *Chem. Rev.*, **115**, 327–394.
124. Nguyen, K.T. and Zhao, Y. (2015) Engineered hybrid nanoparticles for on-demand diagnostics and therapeutics. *Acc. Chem. Res.*, **48**, 3016–3025.
125. Xie, J., Lee, S., and Chen, X. (2010) Nanoparticle-based theranostic agents. *Adv. Drug Deliv. Rev.*, **62**, 1064–1079.
126. Li, J., Gupta, S., and Li, C. (2014) Research perspectives: gold nanoparticles in cancer theranostics. *Quant. Imaging Med. Surg.*, **3**, 284–291.
127. Gautier, J., Allard-Vannier, E., Munnier, E., *et al.* (2013) Recent advances in theranostic nanocarriers of doxorubicin based on iron oxide and gold nanoparticles. *J. Control. Release*, **169**, 48–61.
128. Zhang, Z., Wang, L., Wang, J., *et al.* (2012) Mesoporous silica-coated gold nanorods as a light-mediated multifunctional theranostic platform for cancer treatment. *Adv. Mater.*, **24**, 1418–1423.
129. Lewinski, N., Colvin, V., and Drezek, R. (2008) Cytotoxicity of nanoparticles. *Small*, **4**, 26–49.
130. Derfus, A.M., Chan, W.C.W., and Bhatia, S.N. (2004) Probing the cytotoxicity of semiconductor quantum dots. *Nano Lett.*, **4**, 11–18.

131. Tang, M., Wang, M., Xing, T., *et al.* (2008) Mechanisms of unmodified CdSe quantum dot-induced elevation of cytoplasmic calcium levels in primary cultures of rat hippocampal neurons. *Biomaterials*, **29**, 4383–4391.
132. Warheit, D.B. (2008) How meaningful are the results of nanotoxicity studies in the absence of adequate material characterization? *Toxicol. Sci.*, **101**, 183–185.
133. Asseth, J., Haugen, M., and Førre, O. (1998) Rheumatoid arthritis and metal compounds – perspectives on the role of oxygen radical detoxification. *Analyst*, **123**, 2–6.
134. Conner, E.E., Mwamuka, J., Gole, A., *et al.* (2005) Gold nanoparticles are taken up by human cells but do not cause acute cytotoxicity. *Small*, **1**, 325–327.
135. Mironava, T., Hadjiargyrou, M., Simon, M., *et al.* (2010) Gold nanoparticles cellular toxicity and recovery: Effect of size, concentration and exposure time. *Nanotoxicology*, **4**, 120–137.
136. Alkilany, A.M. and Murphy, C.J. (2010) Toxicity and cellular uptake of gold nanoparticles: what we have learned so far? *J. Nanopart. Res.*, **12**, 2313–2333.
137. Gupta, A.K. and Wells, S. (2004) Surface-modified superparamagnetic nanoparticles for drug delivery: Preparation, characterization, and cytotoxicity studies. *IEEE Trans. Nanobiosci.*, **3**, 66–73.
138. Teske, S.S. and Detweiler, C.S. (2015) The biomechanisms of metal and metal-oxide nanoparticles' interactions with cells. *Int. J. Environ. Res. Public Health*, **12**, 1112–1134.
139. Porter, A.E., Muller, K., Skepper, J., *et al.* (2006) Uptake of C60 by human monocyte macrophages, its localization and implications for toxicity: Studies by high-resolution electron microscopy and electron tomography. *Acta Biomater.*, **2**, 409–419.
140. Cui, D., Tian, F., Ozkan, C.S., *et al.* (2005) Effect of single-walled carbon nanotubes on human HEK293 cells. *Toxicol. Lett.*, **155**, 73–85.
141. Pulskamp, K., Diabatée, S., and Krug, H.F. (2007) Carbon nanotubes show no sign of acute toxicity but induce intracellular reactive oxygen species in dependence on contaminants. *Toxicol. Lett.*, **168**, 58–74.
142. Chung, T.-H., Wu, S.-H., Yao, M., *et al.* (2007) The effect of surface charge on the uptake and biological function of mesoporous silica nanoparticles in 3T3-L1 cells and human mesenchymal stem cells. *Biomaterials*, **28**, 2959–2966.
143. Di Pasqua, A.J., Sharma, K.K., Shi, Y., *et al.* (2008) Cytotoxicity of mesoporous silica nanomaterials. *J. Inorg. Biochem.*, **102**, 1416–1423.
144. Hudson, S.P., Padera, R.F., Langer, R., and Kohane, D.S. (2008) The biocompatibility of mesoporous silicates. *Biomaterials*, **29**, 4045–4055.
145. Chen, Y., Chen, H., and Shi, J. (2013) In Vivo Bio-Safety Evaluations and Diagnostic/ Therapeutic Applications of Chemically Designed Mesoporous Silica Nanoparticles. *Adv. Mater.*, **25**, 3144–3176.
146. Shi, Y., Miller, M.L., Di Pasqua, A.J., *et al.* (2016) Biocompatibility of mesoporous silica nanoparticles. *Comment. Inorg. Chem.*, **36**, 61–80.