Theranostic cancer applications utilized by nanoparticles offering multimodal systems and future insights

Emir Yasun¹

Received: 4 April 2020 / Accepted: 20 August 2020 / Published online: 25 August 2020
© Springer Nature Switzerland AG 2020

Abstract

Recent studies showed that imaging-guided cancer therapeutics have higher success rates so instead of using a single modality, the combination of diagnosis and therapy (theranostic) modalities have simultaneously been employed more often for the cancer treatments. Also, instead of employing single modality, combination of more than one modality for each cancer diagnosis and therapy becomes to be the route for the scientists study in the field of theranostics and applied nanotechnology due to the improved theranostic efficiency. Purpose-oriented fabricated nanoparticles are usually chosen as carriers and contrast agents for those multimodal theranostic systems owing to their unique optoelectronic (optical-electronic) and physical properties. This is a mini review as a general synopsis of the recent applications of nanoparticles as one of the most efficient cancer theranostic agents and future insights for theranostics.

Keywords Theranostics · Multimodal theranostics · Diagnosis · Cancer therapy · Nanotechnology · CRISPR

1 Introduction

Cancer is caused by the uncontrolled abnormal cell proliferation where the abnormal cells grow out of control and spread. This proliferation is usually induced by various changes such as expression levels, posttranslational modifications or genetic mutations in certain proteins (biomarkers) of the cells [1–5]. Since those cell abnormalities happen in molecular levels, molecular diagnostics and therapeutic systems and thereby nanoparticle-based cancer treatments are quite promising and employed.

Nanoparticle-based cancer diagnostics employ various instrumental techniques utilizing optical, magnetic, radioactive and acoustic properties of carrier or contrast agent nanoparticles [6–22]. These particles either have those properties intrinsically (material and shape dependent) or carry those molecules or other nanoparticles that embody them. Also, hybrid nanoparticles consisting of two or more types of different templating or precursor materials can

be fabricated to gain more than one of those properties within one particle system [10]. On the other hand, change in the physical properties of the nanoparticles such as size, shape or shell thickness (in hybrid particles) also lead those properties to change so this tunability can be exploited to comply with the desired application [6, 23, 24]. For example, absorption of the near-IR (NIR) irradiation is quite important in bioimaging applications since this region of the light spectrum is not harmful due to its minimal absorption by the tissues [8, 23, 25]. Thus, tuning the absorption properties of the nanoparticles to that region of the light spectrum can be achieved by changing their physical properties so that they can be employed in NIR imaging systems based on scattering, fluorescence and photoacoustic imaging [8]. Photoacoustic imaging (PAI) is performed by monitoring the generated acoustic waves due to the thermoelastic expansion of the heated tissues targeted and treated by the nanoparticles that are able to convert the energy of the absorbed light to heat under NIR

✉ Emir Yasun, emiryasun@ucsb.edu | ¹Department of Mechanical Engineering and California NanoSystems Institute (CNSI), University of California Santa Barbara, Santa Barbara, CA 93106-5070, USA.

irradiation [8]. Magnetic imaging, in other words, Magnetic Resonance Imaging (MRI) employs superparamagnetic iron oxide nanoparticles (SPIONs) as contrast agents due to their high magnetic susceptibilities and low toxicity in vivo [10, 11]. In MRI, the contrast, being either bright or dark is formed according to the T_1 or T_2 weighted relaxation times where they determine the rate of protons return to their normal spin (recovery) or reach equilibrium (decay), respectively after the rotations of the protons are flipped with the applied magnetic field [12]. Compared to the conventionally used Gadolinium based MRI contrast agents with possible adverse effects (such as brain deposition and nephrogenic systemic fibrosis), large SPIONs (16–200 nm in diameter) can be employed as great contrast agents for T_2 weighted MRI and small SPIONs (2–7 nm in diameter) suit better for the T_1 weighted MRI imaging [11, 12]. Also, hybrid particles that consist of gold and iron oxide can be synthesized to combine the magnetic and desired optical (scattering, acoustic and etc.) properties for multimodal bioimaging [10]. Moreover, porous/mesoporous and hybrid core-shell nanoparticles can be synthesized to entrap different fluorescent and radioactive molecules for bioimaging purposes [13–15]. Instead of using radioactive tracer molecules (i.e. fluorodeoxyglucose) alone, they can be entrapped in a nanoparticle system so that this complex can be used as a more powerful contrast agent for Positron Emission Tomography (PET) where the signal intensities are enhanced by localizing more radioactive tracer molecules [15]. It is also possible that hybrid particle systems loaded with active tracer molecules can offer multimodal imaging systems such as PET/MRI [15–17]. Also, nanoparticles can be used as contrast agents for Computed Tomography (CT or CAT scan) imaging due to their strong X-ray attenuation that lead them to be displayed as bright images [26]. All of these imaging modalities have their own limitations and concerns. For example, there is a concern of radiation dose with CT and its resolution is limited in soft-tissue [18]. MRI provides higher resolution, but its sensitivity is low (in mM levels) [19, 20]. PET is highly sensitive (in pM levels) but its resolution is again limited (in mm levels) [21, 22]. Therefore, employing nanoparticle systems that can offer multimodal imaging modalities facilitate overcoming those limitations and offer more efficient and higher quality imaging.

On the other hand, in order for the active targeting to be achieved, those carrier nanoparticles should be functionalized with recognition ligands such as antibodies, peptides, affinity molecules (i.e. folic acid) and DNAs (i.e. aptamers) specific to the target cancer cell lines [6, 7, 27–30]. Those affinity tags target the specific biomarkers (peptides, glycoproteins and etc.) either on the membrane or inside of the cells. Ligand tethering can be managed either by commonly known covalent bonds such as amide

or thiolate directly with the surface or functional groups present on the surface of those nanocarriers or by electrostatic and physical adsorption on the carrier particle surfaces. Even those affinity tags could be modified with imaging molecules (i.e. fluorescent dyes) [10, 31, 32] or drug molecules (i.e. doxorubicin (DOX)) [10] to contribute to the overall success of the theranostic applications.

In therapeutical applications, nanoparticles can also be used as carriers (either on the surface or in their pores) for the therapeutic molecules such as drugs (i.e. DOX) and DNAs/RNAs (i.e. siRNA) to be transported inside cancer cells [29, 33]. Besides being carriers, their optical properties allow nanoparticles to be used in photon triggered therapies such as photothermal and photodynamic as well. As explained in photoacoustic imaging, in photothermal therapy (PTT), plasmonic nanoparticles can convert the absorbed light energy into heat and if the cancer cells can specifically be targeted by those surface-modified nanoparticles, they can ablate only the cancer cells [8]. In photodynamic therapy (PDT), instead of heat, the absorbed light energy is transferred to molecular oxygen allowing the generation of cytotoxic reactive oxygen species (ROS) such as singlet oxygen, which can oxidize and attack cell parts leading to cell death [34]. Also, exciting magnetic particles with alternating magnetic fields can generate heat as well and this heat can also be utilized for the hyperthermia therapy of cancer [35]. So, nanoparticles can be designed to simultaneously offer hyperthermia therapy (either by PTT or magnetic nanoparticles), PDT and chemotherapy utilizing the entrapped drugs (i.e. DOX), which can improve the outcomes drastically since the synergistic effect between different therapy modalities increase the therapy efficiency compared to when they are used alone. On the other hand, since PAI depends on the same mechanism and is a NIR compatible diagnostic modality, it can also be combined with the therapeutical modalities such as PTT and PDT [36]. Similarly, drug release can be controlled by this heat generation utilizing the heat responsive drug entrapment strategies on the nanoparticles [8] so that chemotherapy can be combined and controlled with the NIR light triggered therapy modalities such as PTT and PDT. Therefore, the multimodal diagnosis and therapeutic systems can be combined within one nanoparticle system if the nanoparticle is capable of offering compatible various theranostic modalities (i.e. MRI and magnetic nanoparticle induced hyperthermia therapy can be combined with chemotherapy by entrapping drugs within the nanoparticle system) [37].

Furthermore, besides those therapeutic modalities mentioned above, the latest genome editing technology, *clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9* (CRISPR-Cas9) offers another type of therapy that allows scientist to remove, add or

change genetic materials at particular locations in the genome [38, 39]. The RNA portion of the CRISPR binds to the targeted DNA sequence in a genome and Cas9 enzyme cuts the genome at this location to make deletions in the genome, but CRISPR can also be engineered to add new DNA sequences as well [39]. This mechanism might prevent and treat diseases by altering the known genes responsible for the diseases. Thus, nanoparticles can also help this technology as discussed below as carrier and delivery agents.

2 Discussion

Thus, following the diagnosis by multiple strategies, also different therapeutical strategies can be applied to cancer cells simultaneously within one nanoparticle-based (either single or hybrid) theranostic platform. The complementary and synergistic behavior of those modalities improve the outcomes and lay foundation for more efficient theranostic platforms.

It seems like single modality platforms are nowadays considered to be simplistic and inefficient unless there is no room for improvement for their applications. However, despite the success in *in vitro* applications, there is still another challenge to be solved, toxicity and adjustment of sufficient doses of these particles both *in vitro* and *in vivo* applications. Sometimes, in order to adjust the physical properties to gain the essential other properties such as optical (i.e. NIR absorptivity), some toxic templating agents are used (i.e. CTAB) in the fabrication process of those nanoparticles [32], which can cause some side effects for the healthy cells as well despite the specific recognition ligand functionalization. Moreover, other particle characteristics such as size, shape surface chemistry and charge may also play a critical role in nonspecific toxicity and increase the complications. So, further precautions should be taken to passivate those adverse effects. On the other hand, the doses of the nanoparticles should be arranged wisely as well. Since, in some *in vivo* applications, it has been observed that nanoparticles could be accumulated in spleen, kidney and liver of the experimental subject, which can adversely affect the functions of those organs [40]. The success in *in vitro* applications might also be due to the excessive usage of those functional nanoparticles, but *in vivo* applications and especially in clinical applications low doses with high efficiencies are essential. This might explain the presence of very limited clinical trials that adopt nanoparticle based multimodal systems.

Besides those challenges mentioned above, there are intrinsic limitations for each modality. For example, photon triggered modalities require the irradiation to reach the certain parts of the body to treat the tumors. However,

NIR laser irradiation can only penetrate up to 10 mm of thickness and this will definitely decrease the success rates of photon triggered therapies if the tumor is located in deeper sections of the body. So the necessity of increasing the dosages, improving the specificity against the tumors and complementing them with different therapeutic modalities will emerge.

The specific ligands targeting the specific cancer cell lines are selected and generated by comparing their binding affinities to the target cancer cells. However, when they are conjugated to a nanoparticle surface, in order to minimize the conformation change impacts (secondary structure) of the surface, spacer molecules (such as PEG, long carbon chains or even poly nucleotides (poly T)) are arranged between the surface and the targeting ligand molecules [27, 33, 41]. On the other hand, in order to increase their retention times and colloidal stability in biological fluids or buffers, also other functional molecules are employed to functionalize the surface of the nanoparticles. All of these should be optimized very well, otherwise another challenge can be faced in biological systems, immunogenicity, in other words, immune response against all these other functional groups and molecules on the surface of the nanoparticles. So fine tuning the size, charge, dose and functional groups on the surface of nanoparticles is quite critical to overcome that challenge.

3 Conclusions and future insights

In summary, as the specific ligands are developed and more functional nanoparticles are fabricated, there is no question that more efficient and successful targeted multimodal theranostic platforms will emerge. However, there should be much more studies conducted *in vivo* so that it may shed some light on the possible and real challenges of the clinical trials, it would be quite a journey since we are in the era of personalized medicine and gene editing. We will probably see more of the targeted nanoparticle-based delivery of therapeutic CRISPR/Cas9 genome-editing elements. This might pave the way of finding a solution to the core of the problem, instead of trying patch treatments which might be temporal with a high reoccurrence chance and with numerous side effects as they are trying to treat the consequences of the problem. However, with personal medicine and gene editing there might be an actual cure in the molecular level so instead of trying to destroy the consequences, the cancer cells, the cells may be taught to be normal again with those emerging technologies. For example, the expression of the proteins responsible for the abnormal growth of the cells could be controlled in this way and they could behave normally again. However, for those technologies

to be successful, as these biological processes were happening in nanoscale levels, there would be still a need for them to be delivered inside the cells or organs efficiently. Therefore, there is still a need for nanotechnology to come up with efficient ways to deliver those technologies inside the cells and this has already started [42]. However, since the intrinsic properties of the inorganic nanoparticles might not be needed extensively, more biodegradable agents with less side effects such as lipid nanoparticles might be the choice of interest for the delivery of those CRISPR genome editing elements [42]. Even though the aim is towards the more biodegradable and biological nanoparticles (i.e. lipid or DNA based) for the delivery, since gene editing is a very recent advancing technology, in order to image the targeted cells, nanoparticles with intrinsic properties are still employed as cargo elements. The same delivery can also be done with carriers such as viruses (such as Adeno-Associated Viruses (AAVs)) as well [43]. However, it is quite hard to engineer the viruses and also it is a very expensive and slow process and due to their small sizes they have relatively low loading capacity. Thus, it seems like nanoparticles are still going to find their place as cargo agents even for very sophisticated advancing therapeutic technologies like CRISPR.

Compliance with ethical standards

Conflict of interest Dr. Emir Yasun states that there is no conflict of interest.

References

- Anderson NL, Anderson NG (2002) The human plasma proteome: history, character, and diagnostic prospects. *Mol Cell Proteom* 1(11):845–867
- Darmanis S, Nong RY, Hammond M, Gu J, Alderborn A, Vanelid J, Siegbahn A, Gustafsdottir S, Ericsson O, Landegren U, Kamali-Moghaddam M (2010) Sensitive plasma protein analysis by microparticle-based proximity ligation assays. *Mol Cell Proteom* 9(2):327–335
- Olsson AK, Dimberg A, Kreuger J, Claesson-Welsh L (2006) VEGF receptor signalling—in control of vascular function. *Nat Rev Mol Cell Biol* 7(5):359–371
- Osborne CK, Hamilton B, Titus G, Livingston RB (1980) Epidermal growth factor stimulation of human breast cancer cells in culture. *Cancer Res* 40(7):2361–2366
- Ariad S, Seymour L, Bezwodna WR (1991) Platelet-derived growth factor (PDGF) in plasma of breast cancer patients: correlation with stage and rate of progression. *Breast Cancer Res Treat* 20(1):11–17
- Gözübenli N, Yasun E, Dilsiz N (2017) Hybrid nanomaterial: biocolloids. *Turk J Biol* 41:673–699
- Ocsoy I, Ocsoy MA, Yasun E, Tan W (2013) Nucleic acid-functionalized nanomaterials. *Nano LIFE* 03(01):1340004
- Yasun E, Kang H, Erdal H, Cansiz S, Ocsoy I, Huang YF, Tan W (2013) Cancer cell sensing and therapy using affinity tag-conjugated gold nanorods. *Interface Focus* 3(3):20130006
- Yasun E (2013) Aptamer functionalized noble metal particles for bioanalytical and biomedical applications. Ph.D., University of Florida, Ann Arbor
- Li C, Chen T, Ocsoy I, Zhu G, Yasun E, You M, Wu C, Zheng J, Song E, Huang CZ, Tan W (2014) Gold-Coated Fe₃O₄ nanoroses with five unique functions for cancer cell targeting, imaging, and therapy. *Adv Func Mater* 24(12):1772–1780
- McCarthy JR, Weissleder R (2008) Multifunctional magnetic nanoparticles for targeted imaging and therapy. *Adv Drug Deliv Rev* 60(11):1241–1251
- Wei H, Bruns OT, Kaul MG, Hansen EC, Barch M, Wiśniowska A, Chen O, Chen Y, Li N, Okada S, Cordero JM, Heine M, Farrar CT, Montana DM, Adam G, Ittrich H, Jasanoff A, Nielsen P, Bawendi MG (2017) Exceedingly small iron oxide nanoparticles as positive MRI contrast agents. *Proc Natl Acad Sci* 114(9):2325
- Wolfbeis OS (2015) An overview of nanoparticles commonly used in fluorescent bioimaging. *Chem Soc Rev* 44(14):4743–4768
- Chen F, Hong H, Zhang Y, Valdovinos HF, Shi S, Kwon GS, Theuer CP, Barnhart TE, Cai W (2013) In vivo tumor targeting and image-guided drug delivery with antibody-conjugated, radiolabeled mesoporous silica nanoparticles. *ACS Nano* 7(10):9027–9039
- Vecchione D, Aiello M, Cavaliere C, Nicolai E, Netti PA, Torino E (2017) Hybrid core shell nanoparticles entrapping Gd-DTPA and (18)F-FDG for simultaneous PET/MRI acquisitions. *Nanomedicine* 12(18):2223–2231
- Yang C-T, Ghosh KK, Padmanabhan P, Langer O, Liu J, Eng DNC, Halldin C, Gulyás B (2018) PET-MR and SPECT-MR multimodality probes: development and challenges. *Theranostics* 8(22):6210–6232
- Forte E, Fiorenza D, Torino E, Costagliola di Polidoro A, Cavaliere C, Netti PA, Salvatore M, Aiello M (2019) Radiolabeled PET/MRI nanoparticles for tumor imaging. *J Clin Med* 9(1):89
- Vannier MW (2009) CT clinical perspective: challenges and the impact of future technology developments. *Conf Proc IEEE Eng Med Biol Soc* 2009:1909–1912
- Vandenberghe S, Marsden PK (2015) PET-MRI: a review of challenges and solutions in the development of integrated multimodality imaging. *Phys Med Biol* 60(4):R115–R154
- Garcia-Figueiras R, Baleato-Gonzalez S, Padhani AR, Luna-Alcala A, Vallejo-Casas JA, Sala E, Vilanova JC, Koh DM, Herranz-Carnero M, Vargas HA (2019) How clinical imaging can assess cancer biology. *Insights Imaging* 10(1):28
- Grueneisen J, Nagarajah J, Buchbender C, Hoffmann O, Schaaarschmidt BM, Poeppel T, Forsting M, Quick HH, Umutlu L, Kinner S (2015) Positron emission tomography/magnetic resonance imaging for local tumor staging in patients with primary breast cancer: a comparison with positron emission tomography/computed tomography and magnetic resonance imaging. *Invest Radiol* 50(8):505–513
- Rampinelli C, De Marco P, Origgi D, Maisonneuve P, Casiraghi M, Veronesi G, Spaggiari L, Bellomi M (2017) Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis. *BMJ* 356:j347
- Hirsch LR, Stafford RJ, Bankson JA, Sershen SR, Rivera B, Price RE, Hazle JD, Halas NJ, West JL (2003) Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. *Proc Natl Acad Sci U S A* 100(23):13549–13554
- Grzelczak M, Perez-Juste J, Mulvaney P, Liz-Marzan LM (2008) Shape control in gold nanoparticle synthesis. *Chem Soc Rev* 37(9):1783–1791

25. Anderson RR, Parrish JA (1981) The optics of human-skin. *J Invest Dermatol* 77(1):13–19
26. Dong YC, Hajfathalian M, Maidment PSN, Hsu JC, Naha PC, Si-Mohamed S, Breuille M, Kim J, Chhour P, Douek P, Litt HI, Cormode DP (2019) Effect of gold nanoparticle size on their properties as contrast agents for computed tomography. *Sci Rep* 9(1):14912
27. Huang YF, Sefah K, Bamrungsap S, Chang HT, Tan W (2008) Selective photothermal therapy for mixed cancer cells using aptamer-conjugated nanorods. *Langmuir* 24(20):11860–11865
28. Filbrun SL, Filbrun AB, Lovato FL, Oh SH, Driskell EA, Driskell JD (2017) Chemical modification of antibodies enables the formation of stable antibody–gold nanoparticle conjugates for biosensing. *Analyst* 142(23):4456–4467
29. Porta F, Lamers GE, Morrhayim J, Chatzopoulou A, Schaaf M, den Dulk H, Backendorf C, Zink JJ, Kros A (2013) Folic acid-modified mesoporous silica nanoparticles for cellular and nuclear targeted drug delivery. *Adv Healthc Mater* 2(2):281–286
30. Oyelere AK, Chen PC, Huang X, El-Sayed IH, El-Sayed MA (2007) Peptide-conjugated gold nanorods for nuclear targeting. *Bioconjug Chem* 18(5):1490–1497
31. Huang YF, Chang HT, Tan W (2008) Cancer cell targeting using multiple aptamers conjugated on nanorods. *Anal Chem* 80(3):567–572
32. Yasun E, Li C, Barut I, Janvier D, Qiu L, Cui C, Tan W (2015) BSA modification to reduce CTAB induced nonspecificity and cytotoxicity of aptamer-conjugated gold nanorods. *Nanoscale* 7(22):10240–10248
33. Qiu L, Chen T, Öçsoy I, Yasun E, Wu C, Zhu G, You M, Han D, Jiang J, Yu R, Tan W (2015) A cell-targeted, size-photocontrollable, nuclear-uptake nanodrug delivery system for drug-resistant cancer therapy. *Nano Lett* 15(1):457–463
34. Lucky SS, Soo KC, Zhang Y (2015) Nanoparticles in photodynamic therapy. *Chem Rev* 115(4):1990–2042
35. Giustini AJ, Petryk AA, Cassim SM, Tate JA, Baker I, Hoopes PJ (2010) Magnetic nanoparticle hyperthermia in cancer treatment. *Nano LIFE*. <https://doi.org/10.1142/s1793984410000067>
36. Bharathiraja S, Manivasagan P, Santha Moorthy M, Bui NQ, Jang B, Phan TTV, Jung W-K, Kim Y-M, Lee KD, Oh J (2018) Photo-based PDT/PTT dual model killing and imaging of cancer cells using phycocyanin-polypyrrole nanoparticles. *Eur J Pharm Biopharm* 123:20–30
37. Torres-Lugo M, Rinaldi C (2013) Thermal potentiation of chemotherapy by magnetic nanoparticles. *Nanomedicine* 8(10):1689–1707
38. Hsu PD, Lander ES, Zhang F (2014) Development and applications of CRISPR-Cas9 for genome engineering. *Cell* 157(6):1262–1278
39. Lander ES (2016) The heroes of CRISPR. *Cell* 164(1–2):18–28
40. Yildirim L, Thanh NTK, Loizidou M, Seifalian AM (2011) Toxicology and clinical potential of nanoparticles. *Nano Today* 6(6):585–607
41. Yasun E, Gulbakan B, Ocsoy I, Yuan Q, Shukoor MI, Li C, Tan W (2012) Enrichment and detection of rare proteins with aptamer-conjugated gold nanorods. *Anal Chem* 84(14):6008–6015
42. Liu J, Chang J, Jiang Y, Meng X, Sun T, Mao L, Xu Q, Wang M (2019) Fast and efficient CRISPR/Cas9 genome editing in vivo enabled by bioreducible lipid and messenger RNA nanoparticles. *Adv Mater* 31(33):e1902575
43. Xu CL, Ruan MZC, Mahajan VB, Tsang SH (2019) Viral delivery systems for CRISPR. *Viruses* 11(1):28

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.