EDITORIAL

Current Challenges and New Opportunities of Hybrid Nanoparticles for Diagnosis and Treatment of Cancer

Ali Tarighatnia [1, 2], Golshan Mahmoudi [3], Mahnaz Kiani [4], Nader D. Nader [5*]

[1] *Department of Medical Physics, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran*

[2] *Research Center for Pharmaceutical Nanotechnology, Tabriz University of Medical Sciences, Tabriz, Iran*

[3] *Medical Imaging Technology Department, School of Allied Medical Sciences, Shahroud University of Medical Sciences, Shahroud, Iran*

[4] *Research Center for Molecular and Cellular Imaging, Tehran University of Medical Sciences, Tehran, Iran*

[5] *Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA*

*Corresponding Author: Nader D. Nader
Email: nnader@buffalo.edu

Received: 05 September 2023 / Accepted: 12 September 2023

Abstract

Hybrid Nanoparticles (NPs) have emerged as promising tools in cancer diagnosis and treatment, offering the potential for early detection and precise eradication of malignant cells by integrating diverse materials. However, navigating this domain's intricacies, limitations, and hurdles underscores the importance of thoughtful decision-making. This editorial provides a comprehensive exploration of the merits and challenges of nanotechnology in the context of cancer diagnosis, therapy, and theranostics. It sheds light on the current applications and delves into the promising prospects in this field. This editorial aims to foster a deeper understanding of the intricacies of designing efficient protocols for hybrid NP production, contributing to advancing cancer management strategies.

Keywords: Hybrid Nanoparticles; Contrast Agents; Cancer Diagnosis; Cancer Treatment.

DOI:

In the realm of nanotechnology, recent breakthroughs in nanoparticle design have ushered in a promising era for the diagnosis and treatment of cancer. Contrast-enhancing nanoparticles have emerged as invaluable assets across a spectrum of imaging modalities, including X-ray-based techniques like Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Ultrasound (US), Nuclear Medicine (NM), and Optical Imaging (OI). These nanoparticles harness their capabilities through high linear X-ray attenuation coefficients, the alteration of longitudinal and transverse relaxation times, and the change of echo intensity, enabling a nuanced differentiation between scattering and absorbing phenomena. In essence, contrast-enhancing nanoparticles play a pivotal role in elevating the sensitivity and specificity of medical imaging modalities, thereby revolutionizing the landscape of disease detection and procedural precision [1, 2].

Recognizing the distinct strengths and weaknesses inherent to each imaging modality, the synergy achieved through their judicious combination is a powerful strategy for mitigating their limitations. By harnessing the potential of hybrid nanoparticles, the accuracy and efficacy of cancer diagnosis are significantly enhanced, as these nanoparticles seamlessly integrate with diverse imaging methods. This amalgamation bolsters the specificity and sensitivity of tumor imaging and ushers in a new era of early cancer detection and targeted therapeutic interventions. Hybrid nanoparticles, with their multifaceted capabilities, stand as promising tools poised to revolutionize the landscape of cancer diagnosis and treatment, offering hope for patients facing various malignancies [3]. These nanoparticles have been synthesized and designed in several diagnostic, therapeutic, and theranostic platforms [4-6].

Hybrid nanoparticles have garnered significant attention in the medical field due to their remarkable attributes, including high biocompatibility, multi-targeting capabilities, real-time diagnostic potential, and efficient therapeutic applications. Their versatility has led to widespread utilization across various medical domains, particularly in drug delivery and imaging [6-8]. Hybrid contrast nanoparticles, formulated by combining two distinct materials, assume pivotal roles in diagnostic and therapeutic contexts. In the realm of diagnosis, these hybrid nanoparticles offer a multifaceted approach capable of enhancing the detection and characterization of cancer lesions through single or multimodality imaging techniques. By leveraging the combination of different metal or non-metal forms, these nanoparticles enhance contrast in CT scans, variation in T1w and T2w signal imaging, improve radiopharmaceutical uptake, increase echo intensity in ultrasound imaging, and facilitate fluorescent imaging. Intriguingly, through precise nanoparticle design, it becomes feasible to simultaneously harness two-mode contrast enhancements in MRI, specifically T1w and T2w imaging, further expanding their diagnostic potential [9].

Dual-modality hybrid nanoparticles offer distinct advantages over their single-modality counterparts, primarily by affording a more comprehensive and nuanced understanding of diseases through integrating two distinct imaging techniques. These versatile hybrid nanoparticles have materialized within various platforms, including MRI/CT, CT/US, MRI/US, and US/OI, each designed to exploit the complementary strengths of the combined modalities. Typically, one of these hybrid nanoparticle components forms the core, while the other serves as the inner or outer coating, allowing for tailored functionality. Moreover, amalgamating two elemental components within these hybrid nanoparticles can confer unique attributes, such as heightened radiation sensitivity or enhanced responsiveness to photothermal and photodynamic therapies, broadening their therapeutic utility. Additionally, hybrid nanoparticles exhibit multifunctional prowess when coupled with chemotherapy drugs, fostering a synergistic approach to disease management [10].

Hybrid nanoparticles offer a distinctive advantage in the realm of MRI imaging by innovatively providing two-mode contrast effects, namely T1w and T2w, which translate into a more precise and informative differentiation between normal and pathological areas. This signal amplification and attenuation enhancement are instrumental in delivering highly accurate diagnostic information. However, a noteworthy challenge arises when amalgamating these two contrasting elements,

primarily attributable to the pronounced magnetic coupling between T1 and T2. To address this intricacy, meticulous consideration must be given to the design of these nanoparticles. Particular layers should be strategically introduced within the core and cladding, and a careful balance in element concentrations is essential to mitigate the compromising effects that might arise [9, 11]. A notable concern for hybrid MRI nanoparticles, typically crafted from a combination of iron oxide and gadolinium, pertains to their interaction within the magnetic field. While they can alter r1 and r2 rates and T1 and T2 relaxation times, their interplay can compromise each other's contrast effects, warranting precise engineering for optimal performance [12].

The burgeoning field of hybrid nanoparticle technologies presents several formidable challenges. Chief among these is the inherent complexity of these structures, comprising diverse materials that profoundly influence structural stability. Additionally, the production of hybrid nanostructures necessitates more intricate and sophisticated technologies, increasing the difficulty of their manufacturing process. Scaling up production to meet clinical demands in industrial settings while maintaining consistent physicochemical properties poses another substantial hurdle. Moreover, these hybrid nanoparticles may incur higher production costs than their single-particle counterparts. In addition, the construction of hybrid nanoparticles, unlike single nanoparticles, often results in size augmentation, leading to heightened interactions with proteins and blood components, potentially impeding the Reticuloendothelial System (RES) and intensifying toxicity concerns. Hence, a meticulous evaluation of their potential toxicity is imperative before mass production. Addressing these obstacles may involve strategies like maintaining constant particle size through material concentration adjustments. Still, the trade-off between size, concentration, and other parameters must be carefully balanced to ensure optimal outcomes [13].

Much like their single-contrast counterparts, biocompatibility is a pivotal challenge in developing hybrid nanoparticle systems. In this context, the intricate nature of hybrid nanocarriers introduces an additional layer of complexity that can further impact biocompatibility and potentially exacerbate toxicity-related concerns. The amalgamation of multiple components within these hybrid structures can give rise to intricate interactions and cumulative effects, potentially intensifying the need for rigorous assessment and optimization of their biocompatibility profiles. Balancing the incorporation of diverse materials to achieve enhanced functionality while ensuring safe and biocompatible outcomes poses a multifaceted challenge in the ongoing pursuit of these innovative hybrid nanocarriers [14].

In X-ray-based imaging, the development of hybrid nanoparticles has a distinct significance due to incorporating two elements featuring disparate atomic numbers. For instance, combinations like bismuth + iodine or gold + iodine are noteworthy for their impact on the mass attenuation coefficients and radiographic density, quantified as Hounsfield units, in Computed Tomography (CT) scans. Specifically, these hybrid nanoparticles introduce a nuanced interplay that can compromise the photoelectric effect, ultimately reducing the Contrast-to-Noise Ratio (CNR). This intricate dynamic highlights the complex relationship between the constituent elements within these hybrid nanoparticles and their influence on the diagnostic precision of X-ray-based imaging, emphasizing the need for meticulous consideration and optimization of these factors in the pursuit of enhanced CT imaging outcomes [15].

While two-modality hybrid nanoparticles, exemplified by MRI/CT hybrids, offer the distinct advantage of providing both T1 and T2 sequences alongside a tomographic image, thereby enabling the comprehensive visualization of organs encompassing bone, air, and soft tissue, they come with inevitable trade-offs. These hybrid nanoparticles exhibit a lower mass attenuation coefficient and exert a relatively milder influence on relaxation times than their single-modality counterparts. Consequently, their capacity to enhance contrast and provide detailed imaging in specific scenarios may be offset by their diminished impact on linear X-ray attenuation and relaxation characteristics, underscoring the importance of careful consideration when selecting imaging modalities to ensure optimal diagnostic outcomes [16, 17].

As previously discussed, specific hybrid nanoparticles, like gold/bismuth and

bismuth/platinum combinations, have demonstrated the capability to augment radio-sensitizing properties while enhancing contrast in CT imaging. However, it is worth noting that compared to single bismuth nanoparticles, these hybrid counterparts have exhibited a lower Sensitivity-Enhanced Ratio (SER). Furthermore, recent reports indicate that bismuth or gold nanoparticles, when considered individually, may boast more robust Photothermal Therapy (PTT) properties when compared to their hybrid counterparts. This underscores the intricate trade-offs and multifaceted considerations involved in the selection of nanoparticles for specific applications, as the unique attributes of each nanoparticle type can significantly influence their performance in different therapeutic and diagnostic contexts [18-20].

Within the realm of hybrid nanoparticles, a profound debate centers around their design in various structural configurations, particularly the influence of distinct shapes like stars, rods, spheres, and more on critical parameters such as efficiency, size, surface charge, and stability. This intricate interplay underscores the need for meticulous consideration of the nanoparticle geometry in tailoring their performance. Moreover, incorporating targeted ligands within these nanoparticles introduces an additional layer of complexity, impacting the parameters mentioned above. The presence of these ligands, designed to achieve specific targeting, further underscores the importance of a holistic approach in nanoparticle design, encompassing structural characteristics and functional modifications to optimize their effectiveness in diverse applications [21, 22].

Hybrid nanoparticles containing chemotherapeutic agents, often referred to as theranostics, tend to be larger in size compared to their single diagnostic nanoparticle counterparts, especially when tailored for targeted applications. This amalgamation of materials exerts an influence on the electron density of the metallic components, affecting the creation of radiographic density and subsequently reducing contrast in imaging modalities. Additionally, the chemical toxicity stemming from combining these nanomaterials necessitates a meticulous evaluation [23]. Furthermore, in the realm of optical imaging, the synthesis of hybrid nanoparticles presents a more intricate challenge when compared to single nanoparticles. Factors such as precise targeting, size regulation, absorbance across different wavelengths and energy levels, and their interaction with biological systems and potential toxicity become paramount considerations. Addressing these issues, including stability and toxicity within the design, alongside the assessment of surface charge and cellular permeability, is imperative to unlock the full potential of these multifaceted hybrid nanoparticles in optical imaging applications.

In summary, the realm of hybrid nanoparticles, while holding immense promise and offering many advantages, presents a formidable set of challenges compared to their single nanoparticle counterparts. These challenges span a broad spectrum, encompassing synthesis complexities, intricate design and manufacturing technologies, elevated costs, nuanced toxicity considerations, morphology variations, surface charge intricacies, blood circulation toxicity, stability concerns, and the critical dimension of biocompatibility. Evidently, a comprehensive and holistic approach is required to address these multifaceted challenges effectively, ensuring that the remarkable potential of hybrid nanoparticles can be harnessed to their fullest extent in the realms of diagnostics, therapy, and medical imaging.

References

1- Ali Tarighatnia, Gurkaran Johal, Ayuob Aghanejad, Hossein Ghadiri, and Nader D Nader, "Tips and tricks in molecular imaging: a practical approach." *Frontiers in Biomedical Technologies*, Vol. 8 (No. 3), pp. 226-35, (2021).

2- Ali Tarighatnia, Mohammad Reza Fouladi, Nader D Nader, Ayuob Aghanejad, and Hossein Ghadiri, "Recent trends of contrast agents in ultrasound imaging: a review of the classifications and applications." *Materials advances*, Vol. 3 (No. 9), pp. 3726-41, (2022).

3- Ali Tarighatnia *et al.*, "Mucin-16 targeted mesoporous nano-system for evaluation of cervical cancer via dual-modal computed tomography and ultrasonography." *New journal of chemistry*, Vol. 45 (No. 40), pp. 18871-80, (2021).

4- Javed Ahmad, Anuj Garg, Gulam Mustafa, Mohammad Zaki Ahmad, Mohammed Aslam, and Awanish Mishra, "Hybrid Quantum Dot as Promising Tools for Theranostic

Application in Cancer." *Electronics*, Vol. 12 (No. 4), p. 972, (2023).

5- Nasim Vahidfar, Ayuob Aghanejad, Hojjat Ahmadzadehfar, Saeed Farzanehfar, and Elisabeth Eppard, "Theranostic advances in breast cancer in nuclear medicine." *International Journal of Molecular Sciences*, Vol. 22 (No. 9), p. 4597, (2021).

6- Behrouz Foroughi-Nia, Jaleh Barar, Mohammad Yousef Memar, Ayuob Aghanejad, and Soudabeh Davaran, "Progresses in polymeric nanoparticles for delivery of tyrosine kinase inhibitors." *Life sciences*, Vol. 278p. 119642, (2021).

7- Ayeskanta Mohanty, Saji Uthaman, and In-Kyu Park, "Utilization of polymer-lipid hybrid nanoparticles for targeted anti-cancer therapy." *Molecules*, Vol. 25 (No. 19), p. 4377, (2020).

8- Ali Tarighatnia, Behrouz Foroughi-Nia, Nader D. Nader, and Ayuob Aghanejad, "Recent trends and advances in nanosystems with tyrosine kinase inhibitors for image-guided cancer treatments." *Journal of Drug Delivery Science and Technology*, Vol. 88p. 104938, 2023/10/01/ (2023).

9- Yurena Luengo Morato, Marzia Marciello, Laura Lozano Chamizo, Karina Ovejero Paredes, and Marco Filice, "Hybrid magnetic nanoparticles for multimodal molecular imaging of cancer." in *Magnetic Nanoparticle-Based Hybrid Materials*: *Elsevier*, (2021), pp. 343-86.

10- Seulki Lee and Xiaoyuan Chen, "Dual-modality probes for in vivo molecular imaging." *Molecular imaging*, Vol. 8 (No. 2), p. 7290.2009. 00013, (2009).

11- Azadeh Amraee *et al.*, "Ultrasmall iron oxide nanoparticles and gadolinium-based contrast agents in magnetic resonance imaging: a systematic review and meta-analysis." *Clinical and Translational Imaging*, Vol. 11 (No. 1), pp. 83-93, (2023).

12- Zahra Bakhtiary, Amir Ata Saei, Mohammad J Hajipour, Mohammad Raoufi, Ophir Vermesh, and Morteza Mahmoudi, "Targeted superparamagnetic iron oxide nanoparticles for early detection of cancer: Possibilities and challenges." *Nanomedicine: Nanotechnology, Biology and Medicine*, Vol. 12 (No. 2), pp. 287-307, (2016).

13- Paniz Siminzar, Mohammad Reza Tohidkia, Elisabeth Eppard, Nasim Vahidfar, Ali Tarighatnia, and Ayuob Aghanejad, "Recent trends in diagnostic biomarkers of tumor microenvironment." *Molecular Imaging and Biology*, Vol. 25 (No. 3), pp. 464-82, (2023).

14- Carolina Salvador Morales, Pedro M Valencia, Anjali B Thakkar, Edward Swanson, and Robert Langer, "Recent developments in multifunctional hybrid nanoparticles: opportunities and challenges in cancer therapy." *Frontiers in Bioscience-Elite*, Vol. 4 (No. 1), pp. 529-45, (2012).

15- Ali Tarighatnia *et al.*, "Engineering and quantification of bismuth nanoparticles as targeted contrast agent for computed tomography imaging in cellular and animal models." *Journal of drug delivery science and technology*, Vol. 66p. 102895, (2021).

16- María Gabriela Montiel Schneider *et al.*, "Biomedical applications of iron oxide nanoparticles: Current insights progress and perspectives." *Pharmaceutics*, Vol. 14 (No. 1), p. 204, (2022).

17- Nasim Jamshidi, Ali Tarighatnia, Mona Fazel Ghaziyani, Fakhrossadat Sajadian, and Nader D Nader, "Folic acid-conjugated Fe-Au-based nanoparticles for dual detection of breast cancer cells by magnetic resonance imaging and computed tomography." *Frontiers in Biomedical Technologies*, (2023).

18- Jamileh Kadkhoda, Ali Tarighatnia, Mohammad Reza Tohidkia, Nader D Nader, and Ayuob Aghanejad, "Photothermal therapy-mediated autophagy in breast cancer treatment: Progress and trends." *Life Sciences*, Vol. 298p. 120499, (2022).

19- Jamileh Kadkhoda, Ali Tarighatnia, Jaleh Barar, Ayuob Aghanejad, and Soodabeh Davaran, "Recent advances and trends in nanoparticles based photothermal and photodynamic therapy." *Photodiagnosis and photodynamic therapy*, Vol. 37p. 102697, (2022).

20- Jamileh Kadkhoda, Ali Tarighatnia, Nader D Nader, and Ayuob Aghanejad, "Targeting mitochondria in cancer therapy: Insight into photodynamic and photothermal therapies." *Life Sciences*, p. 120898, (2022).

21- Keyvan Kheyrolahzadeh, Mohammad Reza Tohidkia, Ali Tarighatnia, Parviz Shahabi, Nader D Nader, and Ayuob Aghanejad, "Theranostic chimeric antigen receptor (CAR)-T cells: Insight into recent trends and challenges in solid tumors." *Life Sciences*, p. 121917, (2023).

22- Ayuob Aghanejad *et al.*, "A review on targeting tumor microenvironment: The main paradigm shift in the mAb-based immunotherapy of solid tumors." *International Journal of Biological Macromolecules*, Vol. 207pp. 592-610, (2022).

23- Seraj Mohaghegh, Ali Tarighatnia, Yadollah Omidi, Jaleh Barar, Ayuob Aghanejad, and Khosro Adibkia, "Multifunctional magnetic nanoparticles for MRI-guided co-delivery of erlotinib and L-asparaginase to ovarian cancer." *Journal of Microencapsulation*, Vol. 39 (No. 4), pp. 394-408, (2022).