**MINI-REVIEW**

**In vivo CT imaging tracking of stem cells labeled with Au nanoparticles**

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**Funding information**
National Key R&D Program of China, Grant/Award Number: 2017YFA0104301; National Natural Science Foundation of China, Grant/Award Number: 81801769; Jiangsu Provincial Fund for Natural Sciences, Grant/Award Number: BK20180257

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**Abstract**
Stem cell–based therapy offers great promise for a wide range of diseases and injuries that cannot be effectively treated by existing medicine and therapies. However, the translation of stem cell therapy to the clinic is still hampered by the lack of profound understanding about the survival, differentiation, migration, homing, and fate of the transplanted stem cells during the therapy. To address these issues, computed tomography (CT) based on nanomaterials, in particular gold nanoparticles (AuNPs), has been developed for enhanced and long-term imaging tracking of transplanted stem cells. In this Mini-Review, we summarize the recent progress in AuNP-based CT imaging tracking of stem cells, with focuses on new strategies to improve cellular uptake of AuNPs for better CT imaging contrast, and on multimodal imaging tracking of stem cells in vivo. Finally, we discuss the existing challenges and possible future developments of the AuNP-based CT imaging tracking of stem cells for regenerative medicine and other biomedical applications.

**KEYWORDS**
computed tomography, gold nanoparticles, imaging, labeling, stem cells, tracking

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**1 INTRODUCTION**

Stem cells have shown great potential for wide applications in biomedical fields, such as cardiology, neurology, orthopedics, and oncology,1,2 owing to their abilities of migrating and homing to the site of disease or injury, secreting therapeutic factors, and differentiating into the target cells.3 However, the main barrier of translating stem cell therapy to clinic is the uncertainty in clinical outcomes, with different patients showing different therapeutic effects after stem cell transplantation. This uncertainty is mainly caused by the lack of a comprehensive and profound understanding of the action mechanism of transplanted stem cells during the treatment process.4 Therefore, it is pressing to develop a noninvasive and real-time cell imaging and tracking strategy to gain an in-depth understanding and evaluation of the delivery, migration, regenerative ability, and final fate of the transplanted stem cells during the treatment.

To address this need, many biomedical diagnostic techniques, such as fluorescence imaging,5 bioluminescence imaging,5 positron emission tomography (PET).7
single-photon emission computed tomography (SPECT), computed tomography (CT) imaging, and magnetic resonance imaging (MRI), to name a few, have been extensively exploited for noninvasive tracking of transplanted stem cells. However, each of these tools has its own unique advantages and limitations. For instance, optical imaging has good imaging sensitivity, while suffering with low tissue penetration depth and resolution. MRI provides a high spatial resolution, but with low sensitivity and long scanning time. PET/SPECT offers high level of sensitivity but with poor spatial resolution. Compared with other imaging technologies, CT remains the dominant imaging technique in both clinic and research because of its good spatial and temporal resolution, high tissue penetration, low cost, short scanning time, and ease of use. Every year, millions of CT scans are performed in clinic all over the world to visualize the anatomical structures of tissues and organs. Especially, CT technique is the top choice of imaging lung tissue in clinical practice owing to the complexity of pulmonary vascular branches and low proton density of lung tissue. To date, CT has been employed in many stem cell–based therapy, for instance, pulmonary fibrosis, retinal disease, bone regeneration, brain disease, and so forth, to monitor the behavior and functions of the stem cells after transplantation. However, the notable drawbacks of CT include its innate low sensitivity and poor image contrast. To overcome these limitations, a variety of materials with high X-ray attenuation, including tungsten, iodine, bismuth, ytterbium, and gold have been explored as contrast agents to label transplanted stem cells and enhance their CT contrast, facilitating their visualization and tracking invivo. In the design of contrast agents for stem cell tracking, several criteria should be taken into consideration. First, the contrast agents should be biocompatible and do not interfere with the cell functions, such as cell viability, migration, and differentiation of labeled stem cells. Second, the contrast agents must maintain their physiochemical stability inside labeled cells. Third, the contrast agents should possess high cell labeling efficiency and imaging contrast to allow detecting and monitoring of transplanted cells in vivo. Last, the contrast agents should have long-term in vivo cell tracking capability. Given the above consideration, gold nanoparticles (AuNPs) have proven to be an ideal CT contrast agent for stem cell tracking due to their good biocompatibility, chemical and physiological stability, and ease of chemical synthesis and functionalization. More importantly, AuNPs exhibit high X-ray attenuation that can provide strong CT imaging contrast of stem cells at a given concentration. However, due to the intrinsic low sensitivity of CT toward contrast agents, large dose of AuNPs per cell is needed for stem cell imaging. Moreover, to get over the shortcomings of individual technique and provide more complementary information of transplanted cells, AuNP-based CT imaging is often exploited in combination with other imaging modalities, such as MRI, fluorescence imaging, bioluminescence (BL), photoacoustic (PA) imaging, to name a few.

In this Mini-Review, we present a brief overview of the most recent significant advancement in AuNP-based CT imaging tracking of stem cells for various biomedical applications (Figure 1). We first introduce the strategies of surface engineering of the AuNPs to increase their intracellular uptake for enhanced cellular CT imaging tracking of transplanted stem cells. We then highlight the design of multifunctional AuNPs for CT-based multimodal cell tracking. Finally, we discuss the current challenges facing the CT imaging tracking of stem cells and future developments in the field.

2 LABELING AND TRACKING STEM CELLS WITH AUNPS

To allow noninvasive CT imaging tracking, the stem cells first need to be labeled with AuNPs. There are typically two approaches to label stem cells: direct and indirect cell labeling. Compared to indirect labeling in which reporter genes are introduced into cells for genetic modification, direct labeling involves co-incubation of the cells with contrast agents in vitro prior to transplantation and has higher biosafety, and is therefore often used for AuNP-based stem cell labeling. Generally speaking, AuNPs are internalized by the cells via endocytosis or phagocytosis during the labeling process. The cellular uptake of AuNPs depends on the size, shape, and surface physicochemical property of AuNPs.

![Figure 1](image.png) Schematic illustration of Au nanoparticle-based in vivo CT imaging tracking of stem cells for regenerative medicine and other biomedical applications.
uptake per cell is required, because CT signal intensity is usually positively correlated with the concentration of contrast agents. Therefore, the key to optimal in vivo imaging of transplanted stem cells is to achieve a maximum amount of AuNP within each cell while ensuring the biological function and viability of the labeled cells for prolonged therapeutic efficacy. To cater for this need, the size and surface nature of AuNPs have to be modified for enhanced cellular uptake and sensitivity of CT imaging.

2.1 | AuNP size-dependent stem cell labeling and tracking

The size of AuNPs imposes important influences on their X-ray attenuation, cellular uptake, and biocompatibility. Xu et al investigated the CT attenuation of AuNPs with different sizes (4, 20, 38, and 60 nm), and found that the smaller AuNPs showed greater X-ray attenuation than the larger ones under the same Au content, attributing to that smaller AuNPs has larger surface area and more dramatic X-ray attenuation (Figure 2A).27 Nevertheless, the CT imaging effect of the labeled cells not only depends on the intrinsic CT attenuation property of the contrast agents, but is also correlated with the content of contrast agents taken up by cells. It has been demonstrated that the size of AuNPs affects their adhesion and interaction with cells, as well as their cellular uptake efficiency and pathways, thus influencing the CT contrast of cells.28 A study by Jiang and colleagues revealed that AuNPs in the range of 40–50 nm formed the critical cutoff point for receptor-mediated internalization, exhibiting the maximum cellular uptake compared with either smaller or larger AuNPs.29,30 Hence, the human mesenchymal stem cells (hMSCs) labeled with 40 nm AuNPs exhibited stronger X-ray attenuation than that labeled with 12 nm AuNPs, even though 12 nm AuNPs displayed significantly higher X-ray absorption than 40 nm AuNPs.6 The size of AuNPs does not only contribute to their different endocytosis rates, but also affects cell viability. Fan et al demonstrated that small-sized AuNPs (3.5 nm) exhibited higher cytotoxicity than large-sized AuNPs (24.4 nm) after incubation with human bone marrow mesenchymal stem cells (hBMSCs).31 Dou group reported that AuNPs exhibited a great size-dependent enhancement on CT imaging contrast in the size range of 3–50 nm (Figure 2B), with the AuNPs of ~13 nm being more suitable for in vivo application due to their superior CT contrast and good biocompatibility.32 Taken together, AuNPs have size-dependent CT attenuation, cell internalization, and biocompatibility. Clearly, big efforts should be made to tune the size of the AuNPs for optimal cellular CT imaging effect.

2.2 | AuNP surface modification-dependent stem cell labeling and tracking

In addition to size, surface modification of AuNPs also alters their aqueous solubility, surface charge, and hydrophilicity, resulting in different cell entry of the nanoparticles. To improve cellular uptake of AuNPs, several strategies, such as using transfection agents or covalently binding an exogenous peptides,33,34 have been developed. Popovtzer et al synthesized glucose modified AuNPs for CT tracking of MSCs. When the cells (1 × 10^6) were incubated with the glucose modified AuNPs (30 μg/mL) for 2 h, approximately 8.8 × 10^−8 mg Au were internalized per cell. More recently, they reported that, after labeling with the glucose-coated AuNPs, as few as 500 cells could be detected by CT imaging with high sensitivity.19,35 In another study, AuNPs were coated with an overlayer of poly-L-lysine (PLL), a cationic transfection agent. The PLL-coated AuNPs exhibited remarkably higher cellular internalization (up to 600 pg Au per cell) (Figure 2C–E), and the labeled hMSCs could be clearly visualized in vitro and in vivo by using a micro-CT scanner, with a detection limit of 2.27 pg Au per cell in vitro, and 2 × 10^4 cells per μL in vivo.9 By coating bovine serum albumin (BSA) stabilized AuNPs with a layer of PLL (Au@BSA@PLL), we recently demonstrated that the uptake of Au@BSA@PLL by hMSCs as high as 293 pg per cell can be achieved, being 1000 times higher than that of Au@BSA and much more than the minimal Au amount (34 pg per cell) required for cellular CT imaging.14,16 In the aforementioned labeling methods, the modification of glucose and PLL endowed the AuNPs with neutral or positive charges, which allowed them to exhibit higher electrostatic force than the negative ones, therefore facilitating their uptake by stem cells. However, high PLL concentration may generate pronounced cell debris and changes in morphology, such as cell lysis, and loss of spindle shape.16 The modification of AuNPs with peptides will achieve good biocompatibility. In a recent work, we used trans-activator of transcription (TAT) peptides to improve the intracellular uptake of AuNPs for better CT imaging tracking of hMSCs.6 Li et al demonstrated that arginine-glycine-aspartate (RGD) modification also facilitated the cell entry of AuNPs through integrin-mediated endocytosis. RGD has negligible negative effect on cellular function, making it a highly biocompatible transfection agent.36 These peptides mentioned above are flexible and movable in biological liquid and have very high affinity to the integrin receptors on cell membrane. Therefore, the peptides conjugated to the AuNPs stimulate clustering of receptor-ligand complexes, strengthen receptor-ligand-mediated signal transduction, and thus improve the intracellular concentration of AuNPs.34,36
2.3 Other factors influencing stem cell labeling and tracking

The labeling process can also be optimized by the incubation time and initial nanoparticle concentration to yield high AuNP uptake. Betzer et al assessed the AuNP taken by three different cell lines, human squamous carcinoma cancer cells (A-431), Human immune cells (T-Cells), and placenta-derived mesenchymal-like adherent stromal cells (PLX-PAD). Their work revealed that the cellular uptake capacity of the AuNP by the three cell types reached the maximum after 1 hour of incubation. However, some cell labeling may take longer incubation time (12-24 h), depending on the types of stem cells and the nature of the AuNPs used. In our study, the hMSCs were incubated with TAT functionalized AuNPs (1 mg/mL Au) for
different duration ranging from 4 to 24 h. Our result displayed that 12 h incubation of AuNPs with the stem cells resulted in maximum cellular uptake of the AuNPs. Another recent study from our group revealed that the intracellular Au contents (10, 25, 81, 158, and 293 pg Au per cell) showed a linear dependence on the concentration of the AuNPs added for labeling (12.5, 25, 50, 100, and 200 μg/mL Au). Clearly, controlling the incubation time and labeling concentration of AuNPs lead to improved cellular uptake of the nanoparticles, but may induce a negative impact on cell viability, proliferation, and differentiation.

In brief, the cellular uptake of AuNPs depends on the size, surface nature, and incubation time and concentration of the AuNPs. From the viewpoint of cell imaging sensitivity and quality, higher amount of AuNPs per stem cell definitely lead to better CT imaging contrast. On the other hand, the amount of AuNP inside each cell should be maintained at a reasonable level, to avoid any adverse effect on the cell survival and functions.

3 | IN VIVO IMAGING TRACKING OF STEM CELLS WITH AUNPS

After being labeled with NPs as contrast agent, the stem cells are injected into animals intravenously or at the site of interest and monitored via appropriate imaging techniques. Studies have shown the feasibility of imaging tracking of stem cells labeled with AuNPs by CT, either alone or in combination with MRI, fluorescence imaging and other diagnostic tools, revealing and elucidating the distribution, migration, and functions of the transplanted stem cells in stem cell therapy.

3.1 | In vivo CT imaging tracking of stem cells labeled with AuNPs

CT, as the leading radiological technology applied in clinic, is a main candidate modality for cell imaging and tracking. To date, many efforts have been paid to explore the visualization of stem cells in vivo using CT imaging. A group led by Popovtzer demonstrated for the first time the application of AuNPs for long-term CT imaging and tracking of stem cells within the brain. In their strategy, MSCs were labeled with glucose modified AuNPs, followed by injection into the brain of a rat model of depression. They unveiled that the MSCs navigated and homed to the distinct depression-related brain region. The cell migration could be detected as early as 24 h and up to one month post-transplantation. As another example, pulmonary fibrosis (PF), a serious lung disease that is difficult to cure with conventional medicine, can be treated effectively with MSCs. To achieve the optimal therapeutic effect and elucidate the mechanism of the stem cells in the lung injury repair, we designed and synthesized a series of AuNPs modified with PLL or TAT, for CT imaging tracking of the transplanted hMSCs in PF model mouse. In our study, we have showed, can deepen our understanding of the role the transplanted stem cells play in the treatment of the damaged lung, thereby offering a useful guidance for developing effective therapeutic strategies.

In another work by Mok et al, 80-nm AuNP labeled MSCs were injected into the rat subretinal layer and successfully tracked the movement of these cells in vivo. The results displayed that the transplant cells could be easily monitored and distinguished from the surrounding endogenous tissue in the rat using micro-CT for up to 30 d. In addition, Meir and his colleagues explored the possibility of noninvasive CT cell tracking using glucose modified AuNPs in a mouse model of Duchenne muscular dystrophy. Interestingly, they observed that with time the labeled cells migrated from the injection site and spread in the muscle.

3.2 | In vivo multimodal tracking of stem cells by combined CT and other imaging techniques

Single imaging modality is often not sufficient to attain all necessary information of stem cells after transplantation. Thus, it is challenging to assess the behavior and functions of transplanted cells using CT alone. The combination of CT with other imaging tools, such as fluorescent imaging, MRI, and BL imaging, can provide complementary information of transplanted stem cells.

In recent years, various types of hybrid AuNPs have been developed for CT-based multimodal imaging tracking of stem cells. In a recent work, we constructed a novel type of multifunctional NPs, gold/gadolinium nanoclusters coated with a silica shell (Au/GdNC@SiO₂), for CT/MR dual-modal imaging tracking of hMSCs in a PF model mouse. The hMSCs labeled with Au/GdNC@SiO₂ exhibited significantly enhanced cellular CT/MR imaging effect because of the silica coating on Au/GdNC surface. Since the detection sensitivity of MRI is much higher than that of CT imaging, at the same concentration of the NPs, MRI signals were much more easily observed than CT signals. The labeled hMSCs transplanted into the lung could be tracked for 7 d via in vivo CT/MR dual modality imaging. Most recently, we developed a CT/fluorescence dual-modal nanotracer to monitor the behavior of BMSCs in the mice with silica-induced PF. In this work, the
AuNPs were first formed in BSA solution, then modified with near-infrared fluorescent dye indocyanine green (ICG), and subsequently coated with a PLL layer, producing AA@ICG@PLL. The AA@ICG@PLL-labeled BMSCs generated CT and fluorescence contrast simultaneously and could be detected for 21 d posttransplantation.

The use of AuNPs for cell tracking is not limited to CT imaging. AuNP-labeled stem cells have been effectively visualized by other imaging modalities, such as PA imaging. In PA imaging, a pulsed laser irradiates an optical absorber, and then, the thermal deposition after absorption causes thermoelastic expansion of the surrounding medium, generating transient acoustic waves. AuNPs can convert absorbed light into heat due to their excellent surface Plasmon resonance properties, making them an ideal contrast agent for PA imaging. Nam et al explored the feasibility of PA imaging for the longitudinal in vivo monitoring of MSCs labeled with AuNPs. They successfully tagged stem cells using gold nanospheres and provided image-guided delivery of stem cells into the spinal cord in real-time, detecting as few as 1000 cells in vivo with high spatial and temporal resolution. PA imaging is usually combined with ultrasound, another technique that can be used for cell tracking applications. Kubelick et al developed an ultrasound/photoacoustic (US/PA) imaging platform using Au nanosphere for long-term tracking of stem cells in anterior eye.

The survival of stem cells after transplantation is a prerequisite for their therapeutical applications, and is often monitored and assessed by transfection of target cells with reporter genes. In our study, we developed a dual labeling strategy integrating AuNPs and red-emitting firefly luciferase for CT/BL multimodal imaging tracking of hMSCs in a mouse model of PF. The combined use of CT and BL imaging techniques enabled in situ visualization of the location, distribution, and survival of the transplanted hMSCs in the lung for 7 d (Figure 2F–G). Recently, Dhada and colleagues made the use of PA imaging to track the survival of transplanted stem cells with a nanoprobe, Au nanorods conjugated with IR775c (a reactive oxygen species sensitive near-infrared dye). In this work, the nanoprobe allowed for longitudinal PA imaging tracking of MSC viability in vivo that other imaging modalities cannot currently achieve.

Overall, it is very important to select and combine different imaging tools for synergistic multimodal imaging tracking of stem cells, largely depending on the specific biomedical applications. We expect that more imaging tools could be combined with CT to elucidate the mechanism of stem cell therapy.

4 | SUMMARY AND OUTLOOK

In this Mini-Review, we briefly summarized the recent advances in AuNP-based CT imaging tracking of stem cells for various biomedical applications. Although significant progress in the field has been made, some major concerns regarding the AuNP-based CT imaging still remain unsolved, which are listed below:

First of all, the signal loss resulted from dilution of the contrast agents in the cells caused by cell division and exocytosis may hamper the long-term CT imaging tracking of stem cells labeled with AuNPs. The possible solution is to rationally design and engineer AuNPs with suitable composition, morphology, surface properties, and even the assembly to improve the CT contrast of AuNPs, and to reduce their exocytosis and dilution caused by cell division.

Secondly, CT tracking of stem cells is useful, but not necessarily and precisely reflect the therapeutical effect of stem cells during the treatment. Therefore, developing multifunctional AuNPs that not only monitor the behavior, but also report the therapeutic effect of the stem cells at the same time can provide sufficient information of transplanted cells and broaden applications of AuNPs in this field. Moreover, drug molecules can be incorporated onto the surface of AuNPs, and thus producing stem cell–based theranostic agents. There are still plenty of untapped possibilities for such combinations to be realized.

Lastly, bioeffect and biosafety of AuNPs used in stem cell labeling and tracking is a prerequisite for their biomedical applications. Despite many studies have demonstrated that AuNPs have negligible impact on the function of stem cells, little is known about how abiotic factors alter the properties of AuNPs with time, and consequently affect the functions of the labeled stem cells. Clearly, more in-depth research should be conducted to uncover the nanoparticle–cell interactions and evaluate the long term toxicity of AuNPs to the stem cells at in vitro and in vivo level.

In conclusion, this Mini-Review presented accounts on the recent advances in the development of various AuNP-based CT contrast agents and their applications in CT-based single- and multimodal imaging tracking of stem cells in vitro and in vivo. Undoubtedly, the rapid development of stem cell–based biomedicine calls for more innovative cell tracking techniques for better understanding of the role the stem cells play in the therapeutical process, thus providing useful guidance to promote the stem cell–based tissue engineering and regenerative medicine, cancer treatment, and beyond.

ACKNOWLEDGMENTS

This work was supported by the National Key R&D Program of China (2017YFA0104301), National Natural
Science Foundation of China (81801769), and Jiangsu Provincial Fund for Natural Sciences (BK20180257).

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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How to cite this article: Huang J, Bao H, Li X, Zhang Z. *In vivo* CT imaging tracking of stem cells labeled with Au nanoparticles. *VIEW*. 2022, 3, 20200119. [https://doi.org/10.1002/VIW.20200119](https://doi.org/10.1002/VIW.20200119)