89Zr-PET Imaging Other than Immuno-PET

Subjects: Oncology

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^{89}Zr is an emerging radionuclide that plays an essential role in immuno-positron emission tomography (PET) imaging. Immuno-PET combines the sensitivity of PET with the specificity of antibodies, and thus is useful for predicting the efficacy of radioimmunotherapy and antibody therapies, imaging target expression, detecting target-expressing tumors, and the monitoring of anti-cancer chemotherapies. PET using ^{89}Zr is not confined to antibody imaging. In this review, we discuss ^{89}Zr-PET applications other than immuno-PET.

Keywords: positron emission tomography ; 89Zr ; monoclonal antibody ; oncological imaging

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^{89}Zr-Labeled Nanoparticles PET

Various radionuclides including ^{198}Au, ^{111}In, ^{64}Cu, ^{125m}Te, ^{188}Re, ^{166}Ho, and ^{99m}Tc have been used for nanoparticle-based nuclear medicine imaging and therapy [1]. Dozens of studies concerning ^{89}Zr-labeled NPs have already been reported, although only a few are clinical. Researchers suggest that ^{89}Zr-labeled NPs (liposomal NPs, nanocolloids, mesoporous silica NPs, dextran NPs, chitosan NPs, etc.) are also promising for tumor detection, the development of nanoparticle drugs, the monitoring of drug delivery, inflammation imaging, and tumor-associated macrophage (TAM) imaging.

TAMs lead to disease progression in cancer cells by modulating the tumor microenvironment and are thus potential targets for anti-cancer therapy. To predict the efficacy of anti-TAM therapy, it is crucial to monitor the quantity and distribution of TAMs. ^{89}Zr-labeled natural high-density lipoprotein (HDL) and dextran NPs showed favorable tumor uptake [2][3]. The co-localization of these radiotracers with a macrophage was revealed by histology and fluorescent imaging [2][3]. These results suggest that ^{89}Zr-labeled NPs can be a good tool for monitoring anti-TAM therapy.

Several studies presented evidence for ^{89}Zr-labeled nanocolloidal albumin as a PET imaging agent for sentinel lymph mapping [4][5][6][7]. In patients with early colon cancers or oral cavity cancers, PET detected sentinel lymph nodes with a very high sensitivity [6][7]. Due to the long half-life of ^{89}Zr, sentinel lymph node mapping using ^{89}Zr-NPs has the advantages of accomplishing both PET imaging and intraoperative probe detection via the single injection of a radiotracer, even though surgical procedures are performed on another day.

^{89}Zr-labeled NPs for atherosclerotic plaques are good examples of inflammation imaging. HDL mimetic infusion has been studied for years as a method to reduce cardiovascular risk. One of the reasons for the failure of HDL mimetic infusion is its low target delivery. ^{89}Zr-labeled natural HDLs and HDL mimetics are delivered to atherosclerotic plaques by being trapped in the macrophages[8][9]. The uptake of ^{89}Zr-labeled HDL mimetics, CER-001, was slightly higher in plaques than in non-plaque walls and correlated well with the contrast enhancement by magnetic resonance imaging (98). Recent animal studies revealed that ^{89}Zr-labeled dextran or hyaluronan NPs have the ability to detect atherosclerotic plaques and monitor anti-inflammatory therapy [10][11].

^{89}Zr-Induced Cerenkov Luminescence Imaging and Therapy

The Cerenkov effect was characterized by Pavel A. Cerenkov in 1934 as the radiation emitted when charged particles (β^+, β^-, α) travel through an optically transparent insulating material with a velocity that exceeds the speed of light. Cerenkov luminescence imaging has been exploited in a number of preclinical studies. The β^+ particles emitted by ^{89}Zr also produce Cerenkov luminescence. Using ^{89}Zr-J591 and luminescence imaging, prostate cancers were visualized in animal models [12].

Photodynamic therapy requires external light to activate the photosensitizers for cancer therapy. Cerenkov radiation from ^{89}Zr can be used as a light source for this purpose. ^{89}Zr-labeled mesoporous silica NPs have ^{89}Zr and photosensitizers inside their hollows. In a breast cancer model, the tumor suppression effect was greater for the ^{89}Zr-labeled mesoporous silica NPs than for the NPs only, or for the control [13]. The advantage of ^{89}Zr over conventional approaches is that ^{89}Zr's long half-life facilitates long-term photodynamic therapy.

Cell Tracking with ^{89}Zr

Due to its old modality, radiolabeled leukocytes, cell tracking is nothing new for nuclear medicine imaging. Thus, it has already been adopted for various types of cell tracking. Using nuclear medicine imaging to evaluate the early distribution and viability of radiolabeled stem cells is a notable example [14]. With the development of cancer immunotherapy, tracking therapeutic cells is becoming more important for predicting the effectiveness of a therapy. ^{89}Zr has a favorable physical half-life for tracking cells in vivo. Additionally, similar to ^{111}In-oxine, ^{89}Zr-oxine can be labeled to cells directly.

Chimeric antigen receptor (CAR) T-cells are transduced to locate specific targets on the surface of tumors. A few drawbacks of CAR T-cells include their poor tumor-targeting ability and normal tissue toxicity [15]. The prediction of therapeutic efficacy by cell tracking is critical to overcome these shortcomings. Direct labeling with ^{89}Zr-oxine allowed the visualization of CAR T-cell migration to tumors in a glioblastoma model [16]. Labeling with ^{89}Zr-oxine did not affect the viability and function of cells. The fragmented antibody $F(ab')_2$ for T-cell receptors is another candidate that showed high sensitivity for T-cells in an animal model. Transduced cells as small as 4.7×10^4 were detected via PET imaging, and the tumor uptake quantity was proportional to the number of injected cells [17].

^{89}Zr-desferrioxamine-N-chlorosuccinimide (DBN) is also actively studied as a direct cell labeling method. Unlike ^{89}Zr-oxine, ^{89}Zr-DBN binds covalently to the amine groups of cell surface membrane proteins [18]. Although the labeling efficiency was low to moderate (30~50%), ^{89}Zr-DBN was stably bound to human mesenchymal stem cells (hMSCs) for up to 7 days without deteriorating the cellular viability [18]. PET imaging using ^{89}Zr-hMSC that were delivered to the adventitia of the outflow vein of arteriovenous fistula allowed to track transplanted hMSCs for 3 weeks [19]. More than 90% of the transplanted cells were detected at the site of delivery on day 4, which was decreased by 20% on day 21 [19]. ^{89}Zr-DBN was also labeled to hepatocytes with a labeling efficiency of 20% [20]. The initial amount of homing cells and the subsequent retention was monitored up to 48 h by PET imaging [20].

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