Dendrimer Nanoparticles Conjugated 99mTc as a Promising Bioimaging Probe

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Abstract

Recent progress in nanoscale tumor targeting may able to deliver radionuclides for improving the outcome of both cancer diagnosis and therapy. Dendrimers are large and complex molecules with well-defined nanoscale structure. Current overview highlights the dendritic nano-probes for Single Photon Emission Computed Tomography (SPECT) because of low sensitivity and specificity. Conjugating radiopharmaceuticals and dendrimers has produced bioimaging probes which have prolonged enhanced stability, reduced toxicity and improved target specificity. However, the application of dendrimers to nuclear medicine is still new technique for improving images. Overall, the multidisciplinary structure of dendrimers makes them good choices for medical imaging or treatment.

Keywords: PAMAM dendrimer; Micro-SPECT imaging; 99mTc radiopharmaceuticals

Introduction

Nuclear medicine agents

In the field of Nuclear Medicine procedures, radio-pharmaceuticals are administered to the patients and their radiations are detected by sensors. In fact, radiopharmaceuticals are consisting of two components, a carrier and a tracer amount of a radionuclide regarding defined radiation types [1]. Routinely, scintigraphy imaging detects the emission of the tracer in a planar form, whereas in Single Photon Emission Tomography (SPECT), the gamma camera detects and reconstructs the tracer emissions as 3D images [2]. Innovative modalities such as Positron Emission Tomography (PET) uses compounds labeled with positron-emitting radionuclides to provide functional images. PET is based on the detection of two photons produced when the positron is emitted from the nucleus of an unstable radionuclide and annihilates with its antiparticle (an electron). PET scanner has higher sensitivity and specificity than SPECT and is able to detect picomolar concentrations of a tracer. PET and SPECT combined with CT scans can compensate the attenuation and provide corrections for emission images with a more accurate anatomical correlation of tracer uptake in the body [3-5]. Moreover, low signal-to-noise ratios (SNR) may make it sophisticated to distinguish targets from the background. The growth of nanotechnology has brought challenging diagnosis and therapy innovations in medicine particularly in the Nuclear Medicine imaging. Consequently, dendrimers in the field of nuclear medicine have concentrated on improving the primary diagnosis of tumors and on their treatment. Conjugating nano-drugs to water-soluble, nontoxic, biocompatible polymers is well established [6-8] which includes long blood circulation time, decreased toxicity [9-13]. Meanwhile, dendrimers are a new class of highly branched spherical polymers that are highly soluble in aqueous solution and have a unique surface of many functional groups. Compared with many other types of dendrimers, Polyamidoamine (PAMAM) dendrimers with huge amine groups have the advantage of conjugating with other molecules via an amide linkage [14,15]. As a challenge in Nuclear Medicine, both SPECT and PET are limited by a low spatial resolution. The main aim of the current review is an assessment of the dendrimers effects on SPECT for improving quality of images. Furthermore, we focused on a wide range of applications of linker molecules for increasing SNR correlated with images.

Molecular imaging modalities

SPECT and PET are two major molecular imaging systems which are used in nuclear medicine. Both techniques use radio-labeled molecules to verification of molecular processes that can be visualized, quantified and tracked over time. The impact of molecular imaging has been on a greater understanding of characterization of disease and detection, and evaluation of treatment [16-18]. SPECT is the most established modality and standard imaging procedures have been widely available. The radiotracers used in SPECT emit gamma rays, as opposed to PET isotopes which are positron emitters like 18F(T1/2=110 min). The SPECT radiotracers have relatively long half-lives from a few hours to a few days (99mTc T1/2=6.0 h; 111In T1/2=67.3 h; 123I T1/2=13.3 h; 201Tl T1/2=72.9 h). As well as an improvement the imaging agents [19,20], focusing on the development of new SPECT imaging systems with increased sensitivity and improve image quality and resolution is a hot topic recently [21].

Image quality

Image quality in Nuclear Medicine, especially in SPECT, is determined by attenuation, scatter, spatial and energy resolution, image noise and contrast. Moreover, numerous studies have demonstrated the integration of CT with SPECT for attenuation correction that improved the image quality, and the CT also provides fair anatomical images [22]. The CT image is obtained prior to the SPECT image and assesses an attenuation map of the spatial distribution of the...
attenuation coefficients. In one hand, patient movement between the two acquisitions can lead to wrong attenuation correction and misregistration. Scatter in SPECT images can reduce image contrast, so various scatter correction algorithms have been reviewed previously [23]. On the other hand, although these algorithms maybe improve image qualities these days nanoparticles application offer a modern technology for this issue. Image quality depends on resolution, sensitivity, a field of view and detector area [24].

Cardiology PET vs. SPECT

The spatial resolution of SPECT is approximately 10 mm while for PET is 5 mm. As a comparison between PET and SPECT studies, despite the challenges of spatial resolution in SPECT, it is shown that SPECT can be a good choice in various clinical applications, especially in cardiology. SPECT is well done in myocardial perfusion imaging. While the guidelines also suggested the use of [18F] FDG PET to assess myocardial viability. Most common 99mTc radiotracers used in cardiovascular imaging shown in Figure 1.

Oncology PET vs. SPECT

PET with multiple radiotracers being used for imaging ([18F] FDG for glucose metabolism, [18F] FLT for cell proliferation, [18F] labeled RGD for angiogenesis, [18F] ethylcholine for prostate, etc.). However, SPECT is used for bone scintigraphy. In a study on the use of [18F] FDG PET vs. SPECT (using 99mTc-HMDP) in detecting bone metastases from breast cancer [25] showed that sensitivity and accuracy of SPECT were more than PET (85%) vs (17%) and (96%) vs (85%) respectively.

Neurology PET vs. SPECT

99mTc-hexamethylpropyleneamineoxime (99mTc-HMPAO) SPECT and [18F] FDG PET is used to detect cerebral perfusion and metabolic abnormalities in Alzheimer’s disease [26]. In neurology, 99mTc is preferred for improved blood-brain barrier penetration as compared to the larger 99mTc SPECT imaging. Common SPECT radiotracers used in neurology was shown in Table 1.

Technetium-99m labeling

Research on 99mTc radiopharmaceuticals commenced after the development of the 99Mo/99mTc generators [27]. The availability of short-lived (half-life: 6h) is a major factor for use of this radioisotope. 99mTc derivatives are used in several diagnostic procedures, from the use of pertechnetate for thyroid uptake to the use of 99mTc-octreotide derivatives for imaging neuroendocrine tumors. A major advantage of 99mTc for radiopharmaceutical development is a varietal chemistry in which making it a good choice to produce many complexes with specific desired characteristics. There are hundreds of 99mTc complexes useful for diagnostic procedures, of which over thirty are used in clinical studies. 99mTc radiopharmaceuticals can be categorized as first, second or third generation products, depending on their level of complexity.

First generation

This generation was employed by taking advantage of the easy absorption, distribution and excretion properties of the 99mTc. Previous studies led to the thyroid (99mTcO4), liver (99mTc-colloids), bone (99mTc-phosphonates) and kidney (99mTc-DTPA) [28].

| Generation | Ammonia core molecular mass/ number of terminal groups | EDA core molecular mass | number of terminal groups |
|------------|-------------------------------------------------------|-------------------------|--------------------------|
| 0          | 359/3                                                 | 516                     | 4                        |
| 1          | 1043/ 6                                               | 1428                    | 8                        |
| 2          | 2411/12                                               | 3252                    | 16                       |
| 3          | 5147/24                                               | 6900                    | 32                       |
| 4          | 10619/48                                              | 14196                   | 64                       |
| 5          | 21563/96                                              | 28788                   | 128                      |
| 6          | 43451/192                                             | 57972                   | 256                      |
| 7          | 87227/384                                             | 116340                  | 512                      |
| 8          | 174779/768                                            | 233076                  | 1024                     |
| 9          | 349883/1536                                           | 466548                  | 2048                     |
| 10         | 700991/3072                                           | 933492                  | 4096                     |

Table 1: Theoretical properties of PAMAM dendrimers.
Second generation

Nuclear magnetic resonance (NMR) spectroscopy, mass spectroscopy (MS) and X-ray diffraction persuade researchers to verify the structure and biological behavior of the $^{99m}$Tc agents and also conjugating other tracers to the $^{99m}$Tc. Consequently, precise design of legends led to the discovery of imaging agents for perfusion in the myocardium and brain. The widely used cardiac imaging agents $^{99m}$Tc-MIBI (sestamibi, Cardiolite), $^{99m}$Tc-tetrofosmin, and the brain imaging agents $^{99m}$Tc-HMPAO (exametazime, Ceretec) and $^{99m}$Tc-ECD (bicisate, Neurilite) are the result of the above strategy in the development of $^{99m}$Tc complexes [29-31].

Third generation

Development these agents led to the labeling the bifunctional chelating agent (BFCA) and new chemistries such as the Tc-tricarbonyl, Tc-nitrido, Tc-HYNIC, $^{99m}$Tc-HYNICEDDA-TOC, developed as an alternative to $^{111}$In-octreotide, and $^{99m}$Tc-TRODAT-1 are the best examples of third generation $^{99m}$Tc radiopharmaceuticals [32,33].

Dendrimers

Dendrimers are nano-sized with a homogeneous and monodisperse structure which is an ideal candidate as targeting nano-objects regarding the vectorization of diagnostic or therapeutic agents through the complexation of very diverse metallic ions [34]. These days, however, the dendrimers are interesting particles for nuclear medicine imaging with attracting a considerable interest to develop novel approaches in cancer imaging, molecular diagnosis.

PAMAM dendrimers

Tomalia et al. synthesized the first generation of Polyamidoamine (PAMAM) dendrimers [35] which have ethylene-diamine (EDA) core and an amidoamine repeat branching structure (Figure 2). They are synthesized via Michael addition of amino groups of EDA with methyl acrylate, followed by admiration of the resulting esters with EDA, and generation 0 is formed (Figure 3). A repetition of these two synthetic steps adds another layer of branching units and produces next generation. The size of dendrimer grows linearly in diameter as a function of added generations, approximately 1 nm per generation (Tables 1 and 2). Each new generation also doubles the number of terminal groups and approximately doubles the molecular weight of the previous generation. Figure 3 shows the synthesis of amine (NH$_2$) terminated PAMAM dendrimers that are cationic; however, there are also neutral hydroxyls (OH) and anionic carboxyl (COOH) terminated PAMAM dendrimers. Due to half completion of the monomer addition, the carboxyl terminated dendrimers are called half generations. Regarding to this issue, dendrimers can covalently attach several drug molecules, targeting groups. For avoiding sterical snag and to provide drug with a reactive group for diagnostic and therapy, a variety of spacer molecules can be linked to the drug and as such used for conjugation reaction with dendrimers. The presence of hydrophilic terminal groups makes dendrimers highly water soluble. The solubility increases with the generation number; the higher generation, the higher number of terminal groups, leads to increased surface charge and polarity. So as will discuss fellow, G2 to G5 dendrimer generations is used for suffering more drug or radiopharmaceuticals in the region of interests for imaging. Physicochemical characteristics of amine-terminated PAMAM dendrimers are shown in Table 1 as well.

Discussion

Regarding the promising dendrimer structure and their valuable properties, numerous researches have offered to design $^{99m}$Tc-labeled dendrimers for diagnostic applications in nuclear medicine. Moreover, the Starburst structure of dendrimers allows multivalent attachment of chelators and targeting moieties. Pioneering work has been carried out by Mukhtar et al [36]. They reported two water-soluble generation (G), G1 and G2 dendrimers, with porphyrin cores possessing terminal iminodiacetic acid groups as chelating moieties for the successful
radiolabeling (95%) with $^{99m}$Tc. Another study was performed by Agashe et al. [37] using this technique to investigate the biodistribution in mice of G5 (polypropylene imine) dendrimers (PPI) coated with mannose (M-PPI) or lactose (L-PPI) so as to explore the potential of these systems as drug carriers. They demonstrated that $^{99m}$Tc-labeled carbohydrate coated dendrimers are cleared from the systemic circulation faster than uncoated dendrimers. Conventional nuclear medicine imaging has low specificity and sensitivity using radiolabeled tumor specific agents. Multiple-step amplification pre-targeting greatly increases the accumulation of radioactivity in the target tissue. One approach to prepare a well-defined of $^{99m}$Tc-labeled dendrimer for SPECT imaging is to incorporate a single high-affinity $^{99m}$Tc ligand at the focal point of high-generation dendrons [38]. Other trials carried out by Shen et al. [39] by involving the G5 PAMAM dendrimers functionalized at the primary amines periphery with DTPA as a $^{99m}$Tc-ligand and folic acid (FA) as a targeting agent for folate receptors over-expressed in cancer cells [40]. Their synthesized radiolabeled PAMAM–FA [conjugate 1] had excellent in vitro/in vivo stability, and the biodistribution analysis in tumor-bearing nude mice indicated its rapid blood clearance and preferential accumulation at the tumor site within 6 hours, which was further confirmed by micro-SPECT imaging (Figure 4).

A subsequent study [41] by the same group demonstrated, both through biodistribution and micro-SPECT imaging studies, that indirect FA conjugation with G5 PAMAM through a PEG spacer increased the tumor uptake. PEG is hydrophilic and structurally flexible, potentially evading the recognition and phagocytosis by macrophage cells in the lymphatic system. This enables folic acid modified with PEG to selectively bind with a metastatic tumor-cell leading to receptor-mediated endocytosis. Such a study confirmed the potential of an FA-conjugated dendrimer as a promising imaging tool for cancer diagnosis (Figure 5).

**Further Applications of Dendrimers**

Many authors with increasing the solubility and decrease the nonspecific cellular uptake suggest the primary amine on the surface of PAMAM dendrimer were partially converted to acetamide moieties in the presence of acetic anhydride and triethylamine [42]. Folic acid (FA) is an optimal targeting ligand for selective delivery of attached imaging and therapeutic agents which has high affinity to the folate receptor [43,44] even after labeling with therapeutic/diagnostic agents and it was used for targeting of FR-positive tumors. The limited distribution of folate receptors in normal tissue makes it an ideal candidate for preferential accumulation and prolonged retention time in tumor tissue due to the impaired lymphatic clearance and cell death in tumor cells.

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**Table 2:** Physiochemical characteristics of amine terminated PAMAM dendrimers.

| Diameter (nm) | Molecular weight | Number of surface groups | Generation |
|---------------|------------------|--------------------------|------------|
| 1.5           | 517              | 4                        | 0          |
| 2.2           | 1430             | 8                        | 1          |
| 2.9           | 3256             | 16                       | 2          |
| 3.6           | 6909             | 32                       | 3          |
| 4.5           | 14215            | 64                       | 4          |
| 5.4           | 28826            | 128                      | 5          |
| 6.7           | 58048            | 256                      | 6          |
| 8.1           | 116493           | 512                      | 7          |
| 9.7           | 467162           | 1024                     | 8          |
| 11.4          | 934720           | 2048                     | 9          |

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Figure 3: Alteration of G0 generation of dendrimers to G1.
of its receptor (FR) in normal tissues and over-expressed in cancer cells made folic acid relatively satisfactory targeting ligand [45]. Recent studies have demonstrated that the conjugation dendrimers with fluorescein may lead to a preferential distribution of the cargo in the targeted tumor cells [46-54]. Emitting fluorescence from dendrimers cannot yet be adapted for clinical use; however, exogenous fluorophores can be conjugated to the exterior primary amine groups to enable detection by the respective imaging modalities. Generation size changes the pharmacokinetic and pharmaco-dynamic properties of dendrimers and increasing the size alter their permeability across the vascular wall, excretion route, and their recognition and uptake by the reticulo-endothelial system. Therefore, smaller sized dendrimers may be used for renal imaging, whereas larger sized preferentially used for imaging the liver and spleen.

Conjugation of FA to the partially acetylated dendrimers was carried out via condensation between the primary carboxylic group of FA and the primary amine of the dendrimer. Zhang et al. have confirmed that synthesized \(^{99m}\text{Tc}\) radio-labeled dendrimer PAMAM-G5-folic acid conjugate showed certain accumulation in KB tumor-bearing nude mice [55]. Their Micro-SPECT imaging further confirmed the conjugate of \(^{99m}\text{Tc}-\text{G5-Ac-FA-1B4M DTPA}\) concentrated in the tumor as time increased and had excellent in vitro/in vivo stability and rapid clearance from blood (Figure 6).

Numerous in vivo studies have demonstrated that 80% of the \(^{99m}\text{Tc}-\text{G5-Ac-FA-DTPA}\) and \(^{99m}\text{Tc}-\text{G5-Ac-DTPA}\) remained intact within 6h in the blood of normal mice [39,55]. Moreover, their biodistribution was investigated with KB tumor-bearing nude mice. For this assessment, the mice were maintained on a folate-deficient diet for the duration of the experiment to minimize the circulating levels of FA. As a result, \(^{99m}\text{Tc}-\text{G5-Ac-DTPA}\) and \(^{99m}\text{Tc}-\text{G5-Ac-FA-DTPA}\) fast cleared from the blood, decreasing from 11.75% injected dose/gram (ID/g) at 2 h to 5.60% ID/g at 6 h for \(^{99m}\text{Tc}-\text{G5-Ac-DTPA}\) and from 12.59% ID/g at 2 h to 4.00% ID/g at 6 h for \(^{99m}\text{Tc}-\text{G5-Ac-FA-DTPA}\). Both agents remained at a low level up to 6 h in the FR-negative organs, including the brain. Micro-SPECT imaging also confirmed the uptake of \(^{99m}\text{Tc}-\text{G5-Ac-FA-DTPA}\) in the FR-positive tumors, liver, and kidneys [39,55]. Investigating on \(^{99m}\text{Tc}-\text{G5-Ac-PEGFA-DTPA}\), \(^{99m}\text{Tc}-\text{G5-Ac-FA-DTPA}\) and \(^{99m}\text{Tc}-\text{G5-Ac DTPA}\) showed that PEGylation of the PAMAM dendrimer-FA conjugate improves the tumor targeting and may be used as a targeted delivery system for imaging labels and therapeutic drugs [41,55].

Parrott et al. have recently developed dendrimers based on aliphatic polyester dendrons labeled with \(^{99m}\text{Tc}\) for dynamic SPECT imaging using rats. It was reported that SPECT images correlated well with data obtained from biodistribution studies. Furthermore, synthesized dendrimers were rapidly cleared from the bloodstream and were nontoxic [56]. Avidin is a quickly internalizing molecule into either normal hepatocytes or cancer cells, especially ovarian and colorectal adenocarcinoma cells, which expresses b-D-galactose receptors [57-61] and extremely easy to conjugate with biotin.

Conjugation of FA to the partially acetylated dendrimers was carried out via condensation between the primary amine of the dendrimer and the free carboxylic group of FA. Zhang et al. have confirmed that synthesized \(^{99m}\text{Tc}\) radio-labeled dendrimer PAMAM-G5-folic acid conjugate showed certain accumulation in KB tumor-bearing nude mice [55]. Their Micro-SPECT imaging further confirmed the conjugate of \(^{99m}\text{Tc}-\text{G5-Ac-FA-1B4M DTPA}\) concentrated in the tumor as time increased and had excellent in vitro/in vivo stability and rapid clearance from blood (Figure 6).

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Xu et al. also evaluated dendrimers as SPECT imaging agents. However, the conjugate containing folic acid molecule has much accumulation in kidneys, so they tried to employ avidin instead of folic acid to observe the biodistribution and micro-SPECT imaging. They synthesized and characterized $^{99m}$Tc radio-labeled acetylated dendrimer–avidin conjugates. The radio-labeled conjugate of Avidin-G5-Ac81-1B4M10-$^{99m}$Tc was successfully prepared and characterized which exhibits excellent in vitro/in vivo stability and rapid clearance from blood. The in vitro cell uptake assay revealed that the conjugate for Avidin-G5-Ac81-1B4M10-$^{99m}$Tc could bind efficiently to HeLa cell, both of the in vivo biodistribution and micro-SPECT imaging study shows that the high uptake was observed in liver and spleen while low in the kidney (Figure 4) [62]. In their study, after receiving the same dose of labeled compound Av-G5-Ac81-1B4M10-$^{99m}$Tc, animals were euthanized at the designated times and selected tissues were removed, weighed, and counted to determine $^{99m}$Tc distribution. The percentages of ID/g in normal mice at 2 h, 4 h and 6 h post-injection of Av-G5-Ac81-1B4M10-$^{99m}$Tc were shown in Table 3.

In addition, acetylated PAMAM (G5-Ac) was conjugated with biotin and 2-(p-isothiocyanatobenzyl)-6-methyl-diethylenetriaminepentaacetic acid (1B4M-DTPA), respectively to form the complex Bt-G5-Ac-1B4M which was further conjugated with avidin to give the conjugate Av-G5-Ac-1B4M. Both of the conjugates were radio-labeled with $^{99m}$Tc, respectively. In vitro cellular uptake study showed that the conjugate of Av-G5-Ac-1B4M-$^{99m}$Tc exhibits much higher cellular uptake in HeLa cells than that of Bt-G5-Ac-1B4M-$^{99m}$Tc [63]. According to these researches about in vitro/in vivo stability, biodistribution and
micro-SPECT imaging was observed only for the conjugate of Av-G5-Ac-1B4M-\(^{99m}\)Tc. In another study, PAMAM dendrimers G4 were labeled with \(^{99m}\)Tc and conjugated with Fluoresceinisothiocyanate (FITC) (Figure 7).

Moreover, dendrimers such as Eu-G3P4A18N, which are build of G3 PAMAM dendrimers may be used in imaging studies for detection of the distribution sites of metastatic hepatic colorectal tumors [64]. Fluorinated dendrimers may act as surfactants in biphasic systems (water/supercritical CO\(_2\)) or as phase transfer catalysts of anionic species from water to supercritical fluids [65,66]. Thanks to the large and well-defined surface area of a dendrimer, they are ideal agents for sensing ions and gases. Metallo-dendrimers are the second type of dendrimers that may be utilized as carriers for catalysts. Furthermore, these types of macromolecules are promising substrates for multielectroreodox processes, photochemistry and photophysics [65]. Catalytic activity present also palladium-based dendrimer-encapsulated metal nanoparticles (DEMNIs) [67] and Cu (II)-PAMAM dendrimers [68]. Photophysical properties exhibit also ionic liquid crystals based on PAMAM and PPI dendrimers (Table 4) [69].

As far as multi-imaging, low-generation dendrimers, G2 maximum, can be used instead of their more complex, time consuming, and high generation contrary. Application of small size dendrimer is beneficial at all of aspects such as, synthetic accessibility, reproducibility and characterization, complete elimination from the body. Therefore, physical size of a dendrimer, which can be controlled by its generation, the charges and hydrophilicity affect the dendrimer’s pharmacokinetics and pharmacodynamics. However, the application of dendrimers to nuclear medicine and radiochemistry is still in its infancy. But rapid technological and scientific progresses in bioimaging, nanomedicine and theragnosis, will provide new research opportunities for biodendrimer scientists in the preclinical and clinical development of new therapies [70].

Recently, Hamidi et al. synthesized aldehyde terminated dendrimers (Polyamidoaldehyde (PAMAL) dendrimers) using aminoacetaldehydedimethylacetal instead of glutaraldehyde and prevent side chain crosslinking problem in producing dendrimers with terminal aldehyde group, successfully. Their research shows that PAMAL has lower toxicity than PAMAM dendrimers in cell cultures (MCF7 breast cancer cell line), which can good choice for diagnostic and especial therapeutics procedures (Figure 8).

SPECT has continued to dominate due to lower cost and use of generator-based radionuclides as compared to PET, which required higher infrastructure cost of cyclotron and radiochemistry facilities. Therefore, better radiotracer design has to be combined with improvements in hardware to improve image quality [71,72].

| Organs          | 2 h     | 4 h     | 6 h    |
|-----------------|---------|---------|--------|
| Blood           | 1.44 ± 0.05 a | 0.91 ± 0.21 | 0.77 ± 0.02 |
| Heart           | 2.48 ± 0.022   | 238 ± 0.75  | 124 ± 0.01   |
| Liver           | 45.55 ± 2.14  | 47.74 ± 1.33 | 56541 ± 130  |
| Spleen          | 43.80 ± 0.50  | 4738 ± 2.00  | 51.09 ± 5.99  |
| Lung            | 12.56 ± 3.02  | 9393 ± 1.81  | 731 ± 292    |
| Kidney          | 2.12 ± 0.17   | 228 ± 0.01   | 335 ± 0.40   |
| Intestine       | 0.84 ± 0.18   | 0.45 ± 0.15   | 0A4 ± 0.06    |
| Stomach         | 022 ± 0.07    | 0.51 ± 0.01   | 0448 ± 0.05   |
| Muscle          | 0.24 ± 0.01   | 0.18 ± 0.05   | 0.16 ± 0.02   |
| Skin            | 0.69 ± 0.26   | 0.57 ± 0.12   | 051 ± 13.08   |
| Bone            | 0.67 ± 0.02   | 0.553 ± 0.09  | 0447 ± 0.01   |
| Brain           | 0.04 ± 0.01   | 0.04 ± 0.02   | 0A5 ± 0.01    |

\(^{99m}\)Values are shown as mean ± SD (id/g)(n=3)

Table 3: Biodistribution of Avidin-G5-AC81-1B4M10 \(^{99m}\)TC 2, 4 and 6 h after injection the tracer in normal mice.

![Figure 7: Scintigraphy image of normal (a) and melanoma-bearing mice (b) injected with \(^{99m}\)Tc (CO)3-dendrimer-FITC, 1 h post-injection. (a) White and yellow arrows point liver and kidneys respectively. (b) White bracket shows the region where the tumor was located. Yellow bracket shows the abdominal region (liver and kidneys) where mask was placed in order to avoid image interference with tumor region. Low uptake observed in surrounding muscle tissues provides good contrast for tumor imaging.](image-url)
Figure 8: Synthesis pathway of aldehyde terminated dendrimers (G2).

### Table 4: Common radiotracers for neurology assessments.

| Target                                      | SPECT radiotracer/ligand                      |
|---------------------------------------------|----------------------------------------------|
| Regional cerebral perfusion                | 62Tc-Tc-bicisate (ECD, Neurorile), 62Tc-exametazime (HMPAO, Ceretec), [123I]ididoamphetamine ([123I]SUIMP) |
| Cerebrospinal fluid kinetics                | [123I]Pentetate                               |
| Phosphatidylserine - dementia               | 62Tc-HYNIC - annexin V                        |
| Dopamine D2, D3 receptors                   | [123I] iodobenzamide (IBZM), [123I]epidepride |
| Dopamine reuptake transporter               | [123I]ioflupane, [123I]al tropine, 62Tc-TRODAT |
| Peripheral benzodiazepine receptor (PBR)    | [123I] PK1119                                 |
| Amyloid                                      | [123I] IMPY                                   |
| Serotonin reuptake transporter (SERT)        | [123I] IDAM, [123I] JADAM                    |
| GABA receptor                                | [123I] dionamizil                             |

### Conclusion

Conjugating radiopharmaceuticals and dendrimers has produced bioimaging probes which have prolonged enhanced stability, reduced toxicity and improved target specificity. However, the application of dendrimers to nuclear medicine is still new technique for improving images. Pharmaceuticals may be encapsulated in dendrimers, physically adsorbed or chemically attached on to the dendrimer surface. Therefore, since these nanoparticles conjugated with radio tracers like 99mTc, quality of images in the region of interest increased. Overall, the multidisciplinary structure of dendrimers makes them good choices for medical imaging or treatment.

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