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RetroSPECT: Gallium-67 as a Long-Lived Imaging Agent for Theranostics

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ABSTRACT

A limitation to the wider introduction of personalised dosimetry in theranostics is the relative paucity of imaging radionuclides with suitable physical and chemical properties to be paired with a long-lived therapeutic partner. As most of the beta-emitting therapeutic radionuclides emit gamma radiation as well they could potentially be used as the imaging radionuclide as well as the therapeutic radionuclide. However, the downsides are that the beta radiation will deliver a significant radiation dose as part of the treatment planning procedure, and the gamma radiation branching ratio is often quite low. Gallium-67 has been in use in nuclear medicine for over 50 years. However, the tremendous interest in gallium imaging in theranostics in recent times has focused on the PET radionuclide gallium-68. In this article it is suggested that the longer-lived gallium-67, which has desirable characteristics for imaging with the gamma camera and a suitably long half-life to match biological timescales for drug uptake and turnover, has been overlooked, in particular, for treatment planning with radionuclide therapy. Gallium-67 could also allow non-PET facilities to participate in theranostic imaging prior to treatment or for monitoring response after therapy. Gallium-67 could play a niche role in the future development of personalised medicine with theranostics.

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Introduction

Theranostic Nuclear Medicine

Nuclear medicine is currently experiencing a great increase in interest clinically, academically and commercially. Much of this has been driven by the introduction of new radionuclide therapies (RNT) that are based on a "theranostic" pair of radionuclides sharing a common label. In the theranostic paradigm, imaging is performed with a suitable radionuclide (SPECT or PET) attached to the label, which could be a molecule, peptide, or monoclonal antibody (mAb), and if sufficient uptake is demonstrated in the target tissues, usually cancerous, a therapeutic radionuclide is substituted for the imaging radionuclide and the patient proceeds to treatment.

Example theranostic pairs currently in use include [^{123}I]/[^{131}I]NaI in thyroid cancer, [^{68}Ga]/[^{177}Lu]DOTA-Octreotate for somatostatin-expressing neuroendocrine tumours (NETs), and [^{68}Ga]/[^{177}Lu]PSMA (Prostate-Specific Membrane Antigen) in prostate cancer. This is not an entirely new concept, with radioiodine having been used in this manner for over 75 years in managing patients with thyroid disease (1).

A major promise of the theranostic approach - yet to be delivered - is to provide a high degree of personalisation in the prescribing of treatment based on the results of the imaging (2). One reason that this has not been realised, is that the

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imaging radionuclide that has been used in the theranostic pair has had very short physical half-life compared to the biological half-life. For example, two of the most commonly used imaging radionuclides are the PET tracers Gallium-68 (^{68}Ga) with a physical half-life of 68 mins and Fluorine-18 (^{18}F) with a half-life of 109.5 mins. The therapeutic radionuclides in a theranostic pairing with these imaging radionuclides usually have much longer half-lives and hence the short-lived imaging tracers give information limited to the early uptake of the theranostic agent alone; they are not able to provide any biodistribution information over an extended period of time. One exception to this is the interesting copper-based theranostic pair Copper-64 (^{64}Cu PET imaging) and Copper-67 (^{67}Cu β^- therapy). The copper-64 imaging radionuclide has a half-life of 12.8 hrs thus permitting extended imaging with a conventional PET camera to 24 hrs after injection and beyond (3). During that period multiple time-point imaging can be performed and subjected to dosimetric analysis to give an individualised estimate of radiation dose delivered (Gy/GBq) so that the amount of therapy to be prescribed can be adjusted to deliver a predetermined amount of radiation to the target tissues, or alternately, to protect organs at risk (4). The therapeutic ^{67}Cu has a physical half-life of 61.8 hrs. Iodine-123 (t½=13.3 hrs) and iodine-131 (t½=8.0 days) as a theranostic pair similarly share advantageous half-life properties.

A limitation to the wider introduction of personalised dosimetry in theranostics is the relative paucity of imaging radionuclides with suitable physical and chemical properties to be paired with a long-lived therapeutic partner. As most of the beta-emitting therapeutic radionuclides emit gamma radiation as well they could potentially be used as the imaging radionuclide as well is the therapeutic radionuclide. However, the downsides are that the beta radiation will deliver a significant radiation dose as part of the treatment planning procedure, and the gamma radiation branching ratio is often quite low. For example, only 11% of nuclear decays of ^{177}Lu produce an imageable photon and, therefore, to follow imaging over an extended period of time (~ days) would require a relatively large amount of radionuclide to be used, which would deliver a degree of treatment prior to knowing whether this was appropriate or not. The desirable characteristics of an imaging radionuclide of a theranostic pair include:

• a half-life of between 1-7 days to match the typical biological scale of the pharmacokinetics;
•significant fraction of photon emissions;
• photon emissions that are suitable for imaging with either the gamma camera (SPECT) or PET camera;
• quantifiable with either SPECT or PET;
• no particle emissions (i.e., α^{2+}, β^-);
• acceptable radiation dosimetry for a diagnostic investigation;
• radiochemical labelling readily achieved;
• high degree of in vivo radiochemical stability;
• readily available;
• relatively inexpensive.

Commonly available imaging radionuclides that do not satisfy one or more of these criteria include ^{18}F, ^{68}Ga, ^{99m}Tc, ^{131}I and possibly ^{177}Lu. Others that have been used and which do meet most of the desirable criteria include ^{64}Cu, ^{86}Y, ^{89}Zr, ^{111}In and ^{124}I. They are, however, relatively expensive to produce and not generally available in large quantities.

Gallium-67 (^{68}Ga) does, however, satisfy a majority of the desirable criteria. Gallium-67 has been in use in nuclear medicine for over 50 years (5) in various roles including cancer-seeking agent (now largely replaced by [^{18}F]FDG PET) and for imaging infectious processes, particularly osteomyelitis and pyrexia of unknown origin (PUO). Infection imaging with gallium-67 is still in regular demand in our clinical department in Sydney, as the Australian government does not provide a service fee for the use of [^{18}F]FDG PET in infection. We still administer on the order of 3-4 [^{67}Ga]Ga-citrate injections per week for the localisation of known or suspected infection, especially for osteomyelitis. It is readily available and relatively inexpensive. Gallium-67 also has the advantage that there is already a large amount of synthetic radiochemistry and chelation technology using radiogallium available based on the popularity of the ^{68}Ge/^{68}Ga generator used in many PET imaging applications.

The aim of this paper is to demonstrate the use of gallium-67 as a near-ideal imaging agent for a theranostic pair by reviewing its physical and chemical characteristics and to show an example of its use in a phase I clinical trial of a potential new theranostic agent.

Physical Properties of Gallium-67

Gallium-67 is a cyclotron-produced radiometal with a physical half-life of 78.3 hrs. It emits up to 10 gamma photons during decay, but the most abundant ones relevant to imaging have energies and relative abundances (%) of 93 keV (39%), 184 keV (21%) and 300 keV (17%). The other photon with reasonable abundance is at 394 keV (4.7%) but is usually not imaged. The three most abundant photons are usually acquired with a triple-pulse height analyser (PHA) approach

summing all photons into a single acquisition frame. They can be acquired separately if necessary. The three photons imaged have an overall abundance of 77%, although their relative detection efficiencies using the NaI (Tl) inorganic scintillator in the gamma camera will vary, with lower energy photons having the higher efficiency. Overall, with a medium-energy collimator in use, our 16 mm thick NaI (Tl) crystal gamma camera (Intevo.6, Siemens Healthineers, Hoffman Estates, USA) has an efficiency of 110 counts/sec/MBq. This compares favourably with Technetium-99m (^{99m}Tc) on the same camera with a low-energy high resolution collimator of ~ 100 counts/ sec/MBq. The spatial resolution is, however, poorer for gallium-67 than technetium-99m because of the medium-energy collimator.

A desirable characteristic for gamma camera imaging today (both 2D planar and 3D SPECT) is the ability to quantify radionuclide distributions in vivo. In a Phase I study of a monoclonal antibody (mAb) directed against GPC-1 ([^{67}Ga]DOTA-Miltuximab® – "MILGa", GlyTherix Ltd, Sydney, AUS), we experimentally established attenuation correction factors for planar imaging based on the MIRD methodology (6) using a cobalt-57 transmission source prior to measuring individual subject-specific transmission factors prior to administering the gallium-67 radiopharmaceutical. The accuracy of the planar whole body radioactivity attenuation-corrected estimate from geometric mean (GM) anterior-posterior imaging was checked early prior to any losses from the body. In twelve subjects, the estimated radioactivity in the body from planar WB imaging soon after calibrated injection of 200 -250 MBq of gallium-67 was in error on average by +3.3% (range: [-1.8%]- [+6.3%]). While planar imaging for individual organ uptake has significant limitations, being able to derive an accurate figure for the total retained radioactivity in the body is extremely useful for dosimetry calculations. While there is not a lot of literature about quantitative SPECT using gallium-67 preliminary work that we have done has demonstrated that this can be accurate, even when summing the three PHA windows into a single image and applying an "effective" attenuation correction factor based on the measured CT data in the SPECT/CT acquisition.

The radiation dosimetry profile for ^{67}Ga-labelled radiopharmaceuticals that have a long biological half-life is not insignificant, due to the prolonged physical half-life of gallium-67 compared to other shorter-lived gamma-emitting radionuclides such as ^{99m}Tc. The most common form of clinical use for gallium-67 is as [^{67}Ga] citrate with an associated Effective Dose of 0.113 mSv/MBq or around 20 mSv for a 185 MBq administration (7). As mAbs have a fairly long biological half-life in vivo, dosimetry from a radiolabelled mAb would be expected to be similar to this figure, although [^{67}Ga]-labelled peptides would be expected to confer a lower dose due to their more rapid biological clearance. In either mode, the dosimetry of gallium-67 as a theranostic imaging agent should not be a concern as the intention is to follow with a radionuclide-based therapy which will deliver many Grays of radiation to the subject – the imaging study constituting only around 1% or less of that radiation dose.

Radiochemistry of Gallium-67

Production of gallium-67 is undertaken by the proton bombardment of an isotopically enriched zinc-68 target at ~ 21 MeV on medium energy (30 MeV) cyclotrons, via the ^{68}Zn (p, 2n) ^{67}Ga nuclear reaction. A number of other production routes are available (8), including natZn (p,xn)^{67}Ga, ^{67}Zn(p,n)^{67}Ga and natZn(d,xn)^{67}Ga (9), but these are not routinely utilised. Chemical purification of gallium-67 from the target material and radioisotopic impurities can be achieved by ion exchange chromatography or solvent extraction, both of which allow recycling of the enriched target (10).

Despite a decline in the number of sites worldwide producing gallium-67 commercially it remains readily available as both the chloride salt, [^{67}Ga] $GaCl_3$ in dilute hydrochloric acid and as the citrate complex, [^{67}Ga] [Ga ($C_6H_5O_5$)2]3- (11) in sterile formulation for human administration. Radiolabelling directly with the formulated citrate complex can be problematic due to the low radioactive concentration 74 MBq/mL (2 mCi/mL) at calibration and presence of excess citrate. However, the formulated citrate complex can be easily converted to the chloride salt in higher activity concentration using a simple silica based SPE method (12).

Gallium (III) is classified as a hard metal with a small ionic radius of 0.62 Å and in aqueous solution it exists solely as redox stable 3+ state. Ga (III) typically adopts octahedral geometries, preferring hard donor atoms such as amine nitrogens and carboxylate oxygens. It is chemically very similar to iron (III), hence its tendency to be taken up by iron proteins, such as transferrin, in vivo. It readily hydrolyses above pH 4 to form ill-defined chemical species and colloids. However, the presence of weakly coordinating ligands such as acetate, citrate or glycinate reduce the propensity to undergo hydrolysis, providing access to a wider useful pH

range (13).

The value of radiolabelling biomolecules was recognised in the mid-1970s with the development of bifunctional chelators based on EDTA (14, 15). This was quickly extended to include DTPA (16). Some of the first examples of gallium-67 and indium-111 labelled antibodies were presented in the early 1980s (17-20) with indium-111 labelled antibodies quickly coming to dominate the field. This is highlighted by the development and FDA approval (in 1996) of [^{111}In] capromab-pendetide (ProstaScint®). Since the early developments, a wide range of chelators have been developed and utilised to prepare radiogallium labelled biomolecules, particularly in the last two decades due to the explosive growth in both the research and clinical use of gallium-68. This topic has been covered in numerous reviews (21-25). Aspects of chelator design and radiolabelling conditions have been optimised to meet the demands of gallium-68, namely rapid labelling to match the short 68 minute half-life. Galllium-67 does not have this kinetic constraint due to the longer half-life so efforts can focus on developing and using thermodynamically stable complexes and mild radiolabelling conditions suitable for sensitive biomolecules. Additionally, thermodynamic stability is likely to be a key factor in the stability of the complex in vivo and resistance towards trans-chelation with transferrin. NOTA (1, 4, 7-triazacyclononane-N, N', N''-triacetic acid) and its derivatives remain the benchmark for ^{67}Ga/^{68}Ga labelling with high thermodynamic stability, mild reaction conditions (25°C, <1 h) and excellent in-vivo stability (26). While the thermodynamic stability constant for Ga(DOTA) (log K=21.3) is significantly lower than that of Ga(NOTA) (log K=31.0) it is worthy of consideration as DOTA-conjugates have direct applicability to therapeutic application with radiolanthanides (^{153}Sm, ^{161}Tb, ^{177}Lu) and other group 3 radiometals such as ^{47}Sc and ^{90}Y. The gallium complex of desferrioxamine (DFO) also has a high stability constant (log K=29.7) (27) and was extensively used in the early developments of radiolabelled antibodies (see above). DFO is also the ligand of choice for most [^{89}Zr] immune PET (28) applications, these agents could easily be adapted to use with gallium-67. Recent studies (29, 30) have demonstrated the utility of the THP (1, 6-dimethyl-3-hydroxypyridin-4-one) chelator for theranostic use of gallium-67 as and imaging and an Auger therapy agent.

The method and chemistry of conjugation also plays a pivotal role in the performance of the antibody-drug conjugates (31, 32). Early studies (33) of [^{67}Ga] DFO-mAbs with three different linkers demonstrated the relationship between linker stability and pharmacokinetic behaviour. Arguably one of the most common methods utilised has been the straightforward acylation of biomolecules, including antibodies, with the anhydride of DTPA (16). However, conjugation strategies have improved and been embellished since this time, particularly recently by the boom in antibody-drug conjugates (34-36) and immunoPET (28, 37) within our own field. The triumvirate of new site-specific conjugation techniques, novel ligands and improved biological vectors signals an opportunity to reinvigorate the development of gallium-67 based radiopharmaceuticals.

Example Using Gallium-67 as Part of a Theranostic Approach

We include an example of the use of gallium-67 attached to a potential therapeutic vehicle. This study was an open label, first-in-human, single centre, Phase I trial conducted at Macquarie University (Sydney, Australia). The study was approved by the Macquarie University Human Research Ethics Committee (Ref: 5201600149) and was registered with the Australian Clinical Trials Registry (ACTRN 12616000787482) and all patients gave informed consent to participate. In this case, the gallium-67 is attached to Miltuximab®, a chimeric mAb targeting cell surface antigen Glypican-1 (GPC-1) (38). GPC-1 is a heparan sulfate proteoglycan (HSPGs) that is not expressed in normal adult tissues but is overexpressed in a range of tumours (39). Pre-clinical studies have demonstrated potential for Miltuximab® as a radioimmunotherapy for solid tumours (40). We undertook the study to assess the safety, tolerability and biodistribution of gallium-67-labelled Miltuximab in patients with advanced solid tumours. The use of a radiotracer with a sufficiently long half-life is important when studying mAbs due to their prolonged retention time in the body and relatively slow pharmacokinetics.

All subjects in the trial had advanced prostate, pancreatic or urothelial carcinoma. In all, 12 subjects were recruited, the preliminary results of which have been reported elsewhere (41). Patients received 200-250 MBq of [^{67}Ga] DOTA-Miltuximab with imaging subsequently at 0.5, 6, 24, 48, 72 and 144 hours post-injection. In this trial we acquired whole-body planar scans and a single SPECT/CT over the abdomen at each time point. Prior to injection, a cobalt-57 transmission scan of the subjects was acquired to allow whole-body dosimetry calculations based on the MIRD-16 formalism (6). Blood samples were also taken for gamma counting at each time point to assist with estimating the bone marrow dosimetry. Figure 1 shows whole body planar (2D),

attenuation corrected geometric mean images of the radiolabelled mAb in one of the subjects in the trial.

Figure 1. Time series of [^{67}Ga] DOTA-Miltuximab® in one of the subjects recruited to the trial. Image quality is excellent at all imaging time point to Day +6 after injection. Only a very small amount of gallium-67 is seen in the urinary bladder or bowel. The amount of retained radioactivity (not corrected for decay) shown in the text under each image was measured for each time point based on the attenuation corrected total radioactivity and a camera-specific sensitivity factor

Discussion

The rapid advances in theranostic nuclear medicine in recent years have primarily concentrated on PET/CT imaging to demonstrate radiotracer avidity in areas of malignancy which can then be followed by treatment using the same targeting vector carrying a particle-emitting radionuclide. The more commonly used PET radiotracers, fluorine-18 and gallium-68, do not, however, have half-lives that are long enough to permit any pre-treatment radiation therapy planning. In this scenario the amount of therapeutic radiopharmaceutical administered is usually based on some empirical or weight-based criteria. Factors such as tumour uptake, retention and radiation doses to organs at risk are generally not available prior to the first treatment cycle. This is in stark contrast with treatment planning in conventional External Beam radiotherapy (EBRT) where dose plans are developed with meticulous attention to detail. It does, however, continue the tradition established with radioiodine ablation and treatment of benign thyroid disorders using, generally, standardised doses that are largely unrelated to the desired amount of energy to be deposited in the target organ (in Gray).

Gallium-67 provides an opportunity to contribute towards more personalised medicine by allowing the study of the theranostic compound prior to commencing therapy. This would involve a protocol that might use a PET/CT scan to demonstrate tumour uptake which is then followed by a gallium-67 labelled study over a number of days, ideally using whole-body SPECT/CT, to allow predictive dosimetry to be determined. The alternative approach is to use the first cycle of treatment, for example using lutetium-177 imaging, to generate similar data. Gallium-67 could also be used in facilities that do not have a PET/CT or PET/MRI camera, thus permitting a wider roll-out for theranostics in the diagnosis, staging, work-up towards treatment and subsequent monitoring of response, albeit with the acknowledged limitations of single photon imaging with the gamma camera. If would be interesting to compare, for example, the imaging performance of [^{67}Ga] DOTA-Octreotate

with [^{111}In] DTPA-octreotide (Octreoscan®) in somatostatin-expressing neuroendocrine tumours.

Quantitative SPECT/CT imaging with radiotracers such as gallium-67 and lutetium-177 is available today (42, 43). A significant limitation on its value in determining lesion dosimetry, however, is the poor spatial resolution in SPECT/CT using a medium energy collimator with values of 20+ mm FWHM in clinical imaging (44). This introduces a significant partial volume effect (PVE) whereby the radioconcentration is underestimated by a significant amount in regions less than "2.5-3x" (times) the spatial resolution, that is, 50-60 mm. While measuring radiation dose in organs such as the kidneys or liver are likely to be largely unaffected by this underestimation, the radiation dose estimates in smaller masses and lymph nodes are likely to be severely impacted to the point where an accurate estimate of likely radiation dose will not be possible. While we are still using the conventional gamma camera based on Anger's original prototype design using a lead collimator it would seem unlikely that hardware developments will provide a solution to this profound underestimate. However, developments in reconstruction algorithms continue apace and techniques such as resolution recovery offer promise that the concentration of radiotracer in objects comparable to the system resolution may be possible (e.g., (45, 46)).

Similarly, there are numerous ongoing developments in the chelation chemistry of gallium compounds. Not mentioned in this article already is the positron-emitting radionuclide gallium-66 which has a 9.5 hr half-life, decays with over 50% by positron emission and can be produced on a medium energy cyclotron by α^{2+} irradiation of a copper target (47). As it is a PET tracer, this isotope of gallium would not suffer from the same spatial resolution limitations that gallium-67 does, however, the half-life would likely preclude imaging beyond 24 hours which may be insufficient for some forms of therapy planning.

The first author (DLB) has argued previously that developments in nuclear medicine technology and methodology often represent physics and chemistry developments "leapfrogging" each other as one gets ahead of the other which then drives innovation for the laggard to catch up (48). The use of gallium-67 as part of a theranostic pair would appear to be an example where methodology has been striving forward but neglecting a tool that is already available. While the radiochemistry developments with gallium-68 have produced many extremely useful radiopharmaceuticals it has also fostered the development of better chelation chemistry for radiometals in general. As the instrumentation and physics of imaging with gallium-67 "catch up" to the advances in the radiochemistry of gallium we will have a readily available source of a near-ideal radiotracer that will prove useful for improving the field of theranostic radionuclide therapy even further. One such example could be to study how the co-injection of a larger mass of "cold" peptide or mAb could modulate or enhance uptake and retention of the radionuclide therapy in target tissues.

Gallium-67 has been largely overlooked in the rush to develop new theranostic approaches. However, it may well find a niche role in the future and certainly in pre-clinical imaging developments of new compounds. In retrospect, we should have recognised its value earlier .

Ethics approval and consent to participate

The example image shown in this manuscript was from an open label, first in human, single centre, phase I trial conducted at Macquarie University Hospital (Sydney, Australia) and Macquarie Medical Imaging (located within Macquarie University Hospital). This study was approved by the Macquarie University Human Research Ethics Committee Ref: 5201600149 and was registered with the Australian Clinical Trials Registry ACTRN12616000787482.

Competing interests

DS, DHC and BJW are employees of GlyTherix Ltd which sponsored the trial from which the example gallium-67 images are shown .

Authors' contributions

DB and NL conceived the concept for the manuscript and wrote the initial drafts.

DS, DHC and BJW oversaw the development of the Ga67-labelled product shown in Figure 1 and contributed to the manuscript related to this activity.

AA contributed to the manuscript preparation in relation to the radiochemistry and has prepared various Ga67-radiolabelled test products.

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