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REVIEW ARTICLE

^{68}Ge/^{68}Ga Generators and ^{68}Ga Radiopharmaceutical Chemistry on Their Way into a New Century

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ABSTRACT

^{68}Ga faces a renaissance initiated by the development of new ^{68}Ge/^{68}Ga radionuclide generators, sophisticated ^{68}Ga radiopharmaceuticals, preclinical research and state-of-the-art clincial diagnoses via positron emission tomography/computed tomography (PET/CT). A new type of ^{68}Ge/^{68}Ga generator became commercially available in the first years of the 21st century, with eluates based on hydrochloric acid. These generators provided 'cationic' ^{68}Ga instead of 'inert' ^{68}Ga-complexes, and opened new pathways of Me^{III} radiopharmaceutical chemistry. The last decade has seen a ^{68}Ga rush. Increasing interest in generator-based ^{68}Ga radiopharmaceuticals in diagnostic applications has been accompanied by its potential use in the context of diease treatment planning, made possible by the inherent option expressed by theranostics. However, widespread acceptance and clinical application requires optimization of ^{68}Ge/^{68}Ga generators both from chemical and regulatory perspectives.

Keywords: ^{68}Ga, ^{68}Ge, Generator, Ligands.

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INTRODUCTION

The ^{68}Ge/^{68}Ga radionuclide generator, with its secular equilibrium mathematics, offers a perfect combination of the nuclidic parameters in terms of half-lives and emission profiles: t½ = 270.95 days for ^{68}Ge and t½ = 67.71 minutes for ^{68}Ga, with no photon emission for ^{68}Ge and an 89.14% positron branching for ^{68}Ga.[10,46] This was known already in the middle of the 20th century, yet gallium-68 today sees a renaissance, with the development of new ^{68}Ge/^{68}Ga radionuclide generators, sophisticated ^{68}Ga radiopharmaceuticals, and state-of-the-art clincial diagnoses via positron emission tomography/computed tomography (PET/CT).[43] Current advances represent a 'renaissance' because ^{68}Ga is one of the very early radionuclides applied to PET imaging. Its application preceeds the use of fluorine-18 and even the term 'positron emission tomorgaphy'. Moreover, the availability of this positron emitter via the first ^{68}Ge/^{68}Ga generators,[16,17] lead to the development of the first positron scintillation camera which was created in the beginning of the 1960s.

With the availability of the first ^{68}Ge/^{68}Ga generators (which provided ^{68}Ga-EDTA eluates) and dramatically improved tomographic detection systems, several ^{68}Ga tracers for imaging of various diseases were investigated (mainly for imaging the human brain). Hundreds of patients were investigated in the USA using ^{68}Ga-EDTA, and others from 1963 on.

Despite several publications describing 'improved' ^{68}Ge/^{68}Ga radionuclide generators, the impact of ^{68}Ga imaging subsided in the late 1970s. This was primarily a consquence of two genertaor-related factors. Firstly, the generator design was inadequate for the versatile synthesis of ^{68}Ga radiopharmaceuticals. Secondly, in view of the parallel and rapid developments of the new classes of ^{99m}Tc- and ^{18}F-labeled diagnostics, the ^{68}Ge/^{68}Ga generators had only minor clinical relevance. Nevertheless, numerous papers in the 1970s and 1980s described the use of inorganic matrixes and organic resins, which allow for the isolation of ^{68}Ga from ^{68}Ge within hydrochloric acid solutions of weak (0.1-1.0 N) or strong (>1 N) concentrations respectively.

Pioneering achievement of radiochemists in Obninsk, Russia, resulted in the development of a new type of ^{68}Ge/^{68}Ga generator which became commercially available in the first years of the 21st century.[40] Generator eluates based on hydrochloric acid provided 'cationic' ^{68}Ga instead of 'inert' ^{68}Ga-complexes, opening new pathways of Me^{III} based radiopharmaceutical chemistry. Initially, the ^{68}Ga cation was introduced into existing ligands used for magnetic resonance imaging (MRI) and SPECT imaging probes, such as DTPA- or DOTA-based derivatives. The impressive results achieved using ^{68}Ga-DOTA-octreotides for PET/CT compared to ^{111}In-DTPA-octroescan paved the way toward the clinical acceptance of this particular tracer for imaging neuroendocrine tracers, and highlighted the great potential of the ^{68}Ge/^{68}Ga generator for modern nuclear medicine in general.

These advances intiated a ^{68}Ga rush in recent times (post 2002). However, the widespread acceptance and clinical application of ^{68}Ga radiopharmaceuticals requires optimization of ^{68}Ge/^{68}Ga generators both from chemical and regulatory points of view. Furthermore, dedicated chelators are required to broaden the possibilities of ^{68}Ga labeling to allow the use of more sensitive targeting vectors. Last but not least, this should also involve applying the concept of ^{68}Ga-radiopharmaceutical chemistry to an increasing number of targeting vectors, addressing the clinically most relevant diseases.

With current innovation and the favorable properties of the ^{68}Ga radionuclide, it is possible that in another decade from now ^{68}Ge/^{68}Ga generator-based ^{68}Ga diagnostics may approach a top three ranking in imaging (together with ^{99m}Tc- and ^{18}F-based tracer diagnostics).

This paper includes material which was presented at the 1st World Congress on Ga-68 and peptide receptor radionuclide therapy (PRRNT) theranostics-on the way to personalized medicine, Bad Berka, Germany, Junge 23-26, 2011, and which were published at a later stage.[5]

THE EARLY YEARS (1960-1970): THE SUNRISE OF ^{68}Ga

The First ^{68}Ge/^{68}Ga Radionuclide Generators

The first ^{68}Ge/^{68}Ga radionuclide generator was described in 1960[16] and entitled: 'A positron cow'. As the title elicits, the concept was to use a radionuclide generator for the production of a positron emitting radionuclide. The latter was a new entry for radiopharmaceutical chemistry and nuclear medicine molecular imaging *in vivo*. The generator chemistry involved a liquid-liquid extraction, and the whole processing protocol was considerably different to that of current radionuclide generator systems. Nevertheless, a variety of ^{68}Ga compounds were synthesized using this generator design.[2,7,44]

Further Generator Developments: Al_2O_3-based EDTA-Eluted Generators

Inherent disadvantages of the first generator lead to the development of two improved generator concepts soon after. The liquid-liquid extraction chemistry introduced by Gleason was substituted for a solid phase-based ion exchange system[17,50] (Fig. 1). In addition, a generator featuring an improved liquid-liquid extraction was described later.[15]

The original sketch, taken from the original publication by Yano and Anger (1964) for the second solid-phase based generator is reproduced in Figure 2. These solid-phase chromatographic generators offered excellent radiochemical characteristics. Using an alumina column and EDTA as eluent (10 ml 0.005 M EDTA), ^{68}Ga was easily eluted in a reproducible 95% yield without the need to introduce stable Ga^{III} as carrier. The eluate contained as little as 1.4×10^{-5}% of the parent ^{68}Ge. Prior to *in vivo* injection, 0.5 ml of 18% NaCl solution was added to the eluate.

^{68}Ge/^{68}Ga Generators and the Development of Positron Scintillation Cameras

This system served as a convenient and economical source of ^{68}Ga-EDTA. Effectively, this radionuclide generator was a synthesis unit of a relevant radiopharmaceutical; ^{68}Ga-

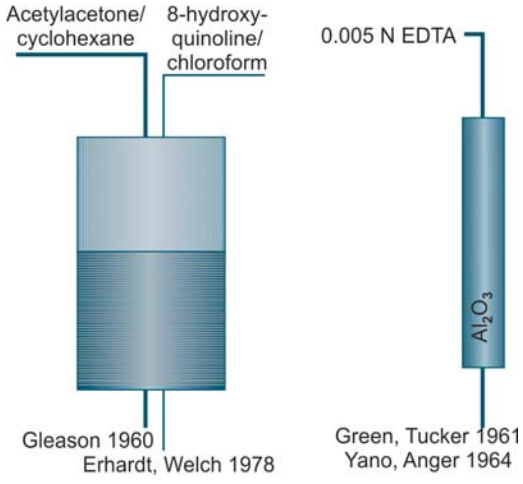

Fig. 1: Early progress in ^{68}Ge/^{68}Ga radionuclide generators II: From liquid-liquid extraction to solid phase-based elution

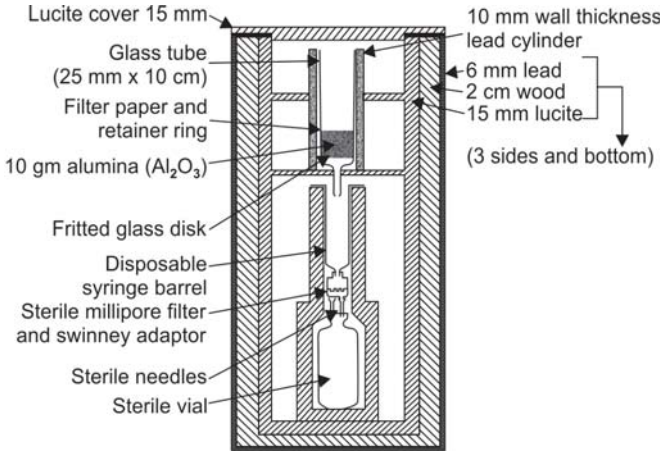

Fig. 2: Solid phase-based (alumina) ^{68}Ga elution (using an EDTA solution) reproduced from the original publication by Yano and Anger (1964)

EDTA (named 'veronate' at the time). ^{68}Ga-EDTA, and limited other ^{68}Ga-tracers, were adapted for human application quite quickly by various groups in the United States for early applications.[20,21,44] Systematic application for brain imaging was reported, with medical impact having significant dependence on the method of detection applied. Conventional imaging appeared to be relatively difficult, with relatively high dosage of ^{68}Ga-EDTA required for valuable medical information to be gained.

Anger thus, started to develop the basics of positron imaging tomography[2,22,23] (arguing as follows (Gottschalk and Anger 1964): … 'We seriously question whether satisfactory results can be obtained with the conventional positron scanner. Recent phantom studies indicate that the positron scintillation camera using ^{68}Ga-EDTA will detect lesions 1/2 the volume that can be detected by the conventional positron scanner using As74. The increase in sensitivity is obtained even though the phantom was set up to simulate our clinical condition where brain pictures are

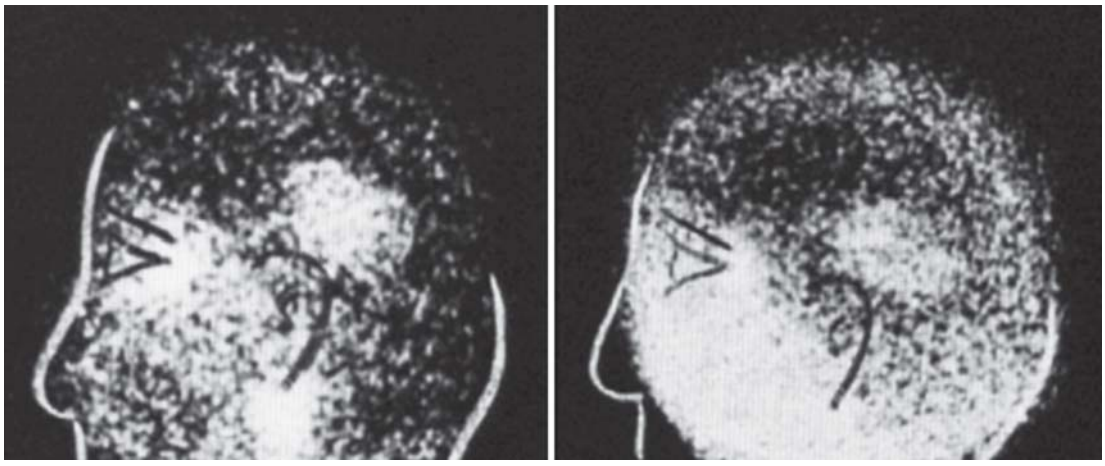

Fig. 3: A ^{68}Ga-EDTA brain scan acquired with the Anger positron camera circa 1962 showing the tomographic capability. The brain tumor is in best focus in the left image, taken at about the level of the temporal horn[2]

obtained in 4 to 10 minutes with a dose of 350 to 750 microcuries of ^{68}Ga-EDTA. Shealy et al, however, found that 2 to 3 millicuries of ^{68}Ga-EDTA was sometimes an inadequate dose with their positron scanner.' Images recorded with this new type of camera (Fig. 3)[2] paved the way for routine PET imaging.

^{68}Ga-EDTA: The Prototype PET-Pharmaceutical

Despite these new imaging features and the great success of ^{68}Ga-EDTA molecular imaging, the fact that in practice the generator was limited to ^{68}Ga-EDTA was a severe limitation. The extraction of ^{68}Ga from the thermodynamically very stable (log K = 21.7) ^{68}Ga-EDTA eluate species was not straightforward. Yano and Anger 1964 reported that, 'attempts are being made. .. to free ^{68}Ga ... from the EDTA complex'. A procedure was developed however; it was not user friendly and practical for ^{68}Ga. On a scale which uses 10 mg Ga carrier, the time required for extraction is 30 minutes, and the transfer yield of 60%.[50] The protocol was:

1. The cow is milked with 10 ml of 0.005 M EDTA solution, and the ^{68}Ga is collected in a 40 ml centrifuge tube.
2. The 10 to 20 mg of carrier $GaCl_3$ in HCl solution is added.
3. The 0.5 ml of saturated ammonium acetate solution is added.
4. Concentrated NH_4OH is added dropwise (about 1 ml) to precipitate $Ga(OH)_3$ at pH 6.0.
5. The solution is heated in a boiling water bath for 10 minutes to coagulate the $Ga(OH)_3$.
6. The solution is centrifuged, and the supernatant solution is discarded.
7. The $Ga(OH)_3$ is dissolved with a minimum volume of hot 20% NaOH.
8. The solution is acidified with about 1 ml of concentrated HCl.

HIBERNATING ^{68}Ga MEDICAL APPLICATIONS, BUT NEW CHEMISTRY AHEAD

The impact of ^{68}Ga imaging started to subside in the late 1970s, for two main reasons. Firstly, the generator design was inadequate in terms of the requirements for versatile synthesis of ^{68}Ga radiopharmaceuticals. Secondly, in view of the parallel and rapid developments of the new classes of ^{99m}Tc- and ^{18}F-labeled diagnostics, the generators available through the existing technology had only minor clinical relevance.

Despite this apparent decrease in interest, numerous basic radiochemical papers in the 1970s and 1980s described the use of inorganic matrixes as well as organic resins, selectively adsorbing ^{68}Ge and providing ^{68}Ga desorbtions within hydrochloric acid solutions of weak (0.1-1.0 N) or strong (>1 N) concentrations respectively.

Cationic ^{68}Ga eluates are required to facilitate the versatile radiolabeling chemistry with ^{68}Ga. Thus, the primary challenge is the development of separation systems which provide cationic ^{68}Ga species. Ga^{III} exists as cationic species (either pure water-hydrated aquocomplexes, such as the hexa-aqua cation $Ga(H_2O)_6^{3+}$, or similar monochloro or monohydroxo species). This speciation is easily achieved in solutions of hydrochloric acid of pH ranging between 0 and 2 (0.01-1.0 N HCl). For this purpose, $Me^{IV}O_2^-$ type matrixes (Me = Sn, Ti, Zr, Ce, etc.) appeared to be adequate, because they effectively adsorb the parent radionuclide $^{68}Ge^{IV}$.[1,25,26,33,39] Alternatively, organic resins have been developed which require more concentrated HCl soltuions for eluting the ^{68}Ga.[3,45] Figure 4 gives a schematic overview.

COMMERCIAL 'IONIC' GENERATORS

Generator Eluates Delivering the Gallium Cation

Thanks to the pioneering achievement of radiochemists in Obninsk (Russian Federation), a new type of ^{68}Ge/Ga

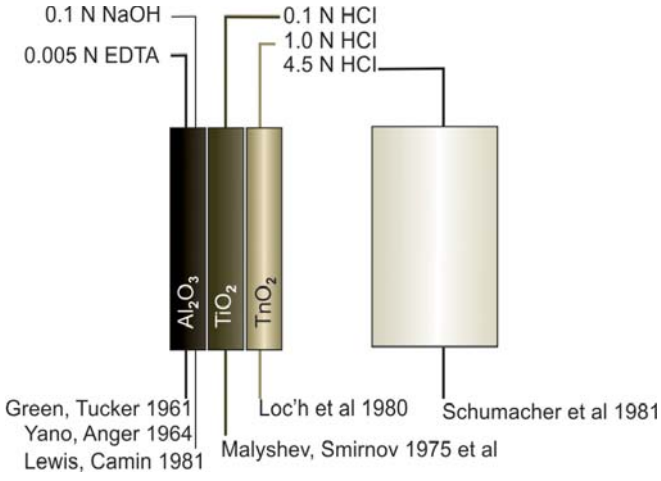

Fig. 4: ^{68}Ge/^{68}Ga radionuclide generator concepts developed in the 1970s and 1980s toward 'cationic' generators

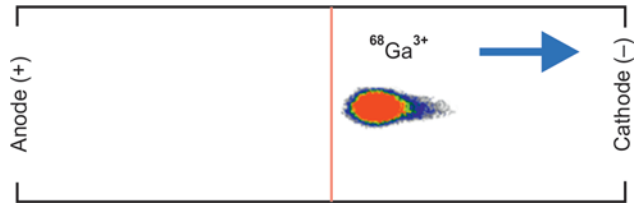

Fig. 5: Electrophoresis of a 0.1 N HCl ^{68}Ga generator eluate (EZAG Obninsk generator) demonstrating the presence of 'cationic' ^{68}Ga (parameters: 0.1 HCl, Whatman® paper strip, l = 19 cm, t = 5 minutes, 191 V, 210 mA, 40 W)

generator became commercially available in the first years of the 21st century.[40] These generators use eluting soltuions based on hydrochloric acid which provide 'cationic' ^{68}Ga, as opposed to 'inert' ^{68}Ga-complexes, opening new pathways of Me^{III}-based radiopharmaceutical chemistry (Fig. 5).

The ^{68}Ga cation was immediately introduced into existing ligand designs of MRI and SPECT imaging probes, namely DTPA- or DOTA-based derivatives. The impressive success of utilizing ^{68}Ga-DOTA-octreotides and PET/CT instead of, e.g. ^{111}In-DTPA-octroescan paved the way for clinical acceptance of this particular tracer for imaging neuroendocrine tumors, but also to the realization of the great potential of the ^{68}Ge/^{68}Ga generator for modern nuclear medicine in general. While commercial 'ionic' generators had successfully entered clinical environments, there were questions regarding its suitability, which became more relevant. In particular these related to its adequacy concerning radiation safety, legal requirements and labeling of medical tracers became more and more relevant. The most relevant concerns are outlined:

- *Problem 1:* The long physical half-life of the parent in principle should give a generator shelf-life of at least 1 year. However, the shelf-life of the generators did not necessarily parallel this long physical half-life due in particular to increasing breakthrough of ^{68}Ge, but also decreasing ^{68}Ga elution yield. ^{68}Ge breakthrough reduction and/or removal of ^{68}Ge from the eluates therefore remain an important radiochemical challenge.
- *Problem 2:* ^{68}Ga generator eluates are not chemically or radiochemically pure. Nonradioactive metals, such as $^{68}Zn^{II}$ (as generated on the generator as decay product of ^{68}Ga), Fe^{III} as general chemical impurity, and $^{68}Ge^{IV}$ as breakthrough represent metals, which may compete with $^{68}Ga^{III}$ for coordinative labeling of radiopharmaceutical precursors. Again, this illustrates the importance of minimizing the ^{68}Ge content in the eluate.[4,51]
- *Problem 3:* The new generation of ^{68}Ge/^{68}Ga radionuclide generators utilize hydrochloric acid solutions for ^{68}Ga elution. The relatively acidic environment created many protonated functional groups of ligands and bifunctional ligands needed for the labeling of ^{68}Ga, which may hinder efficient radiolabeling. Finally, minimizing the pH and volume of ^{68}Ga eluted prior to labeling should facilitate higher radiolabeling yields.

Generator Post-Processing

Three approaches have been developed to address one or more of these problems. Two processes include chemical separation strategies, which may be referred to as 'post-processing'.[35,51] The third technology involves a simple fractionation of the eluate, i.e. isolating eluate fractions with highest ^{68}Ga concentration.[11] The methods are schematically illustrated in Figure 6.

In most cases, commercial generators are used in direct connection with one of the three postelution processing technologies mentioned. The cation exchange-based post-processing[4,51] guarantees almost complete removal of the metallic impurities, in particular ^{68}Ge. Numerous modifications have been reported, including NaCl solutions instead of the solution no. 2 to desorb ^{68}Ga from the resin,[36] or by incorporating a subsequent anion exchange-based purification step[32] to remove organic solvent prior to labeling.

CURRENT STATE/OUTLOOK

Today, ^{68}Ge/^{68}Ga radionuclide generators are commercially available as TiO_2–, SnO_2– or organic resin-based columns. ^{68}Ga eluate yields range from about 70 to 80% for fresh generators, with a decrease overtime. ^{68}Ge breakthrough levels vary between 0.01 and 0.001% (or even less) for fresh generators, with these percentages increasing over extended periods of generator usage. Conjugated with post-processing

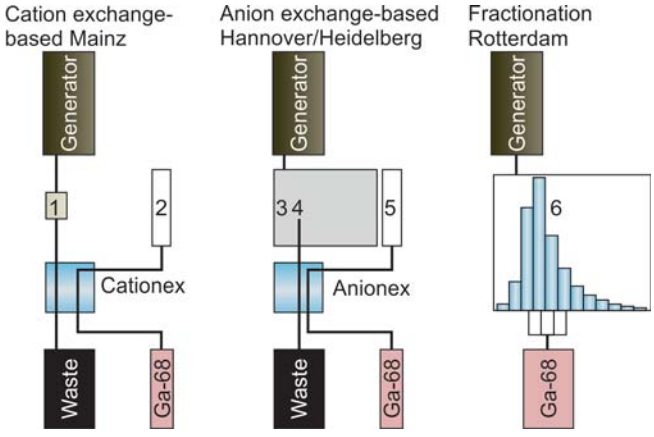

Fig. 6: Schematic representation showing an overview of post-processing technologies for commercial $^{68}Ge/^{68}Ga$ radionuclide generators: (1) Direct generator elution through cation-exchange cartridge, (2) desorption of purified ^{68}Ga using HCl/acetone or HCl/ethanol mixtures, (3) generator elution into HCl reservoir, (4) subsequently elution through anion-exchange cartridge, (5) desorption of purified ^{68}Ga using water, (6) identification of the eluate fraction representing at least two-third of the ^{68}Ga activity, and use without further purification

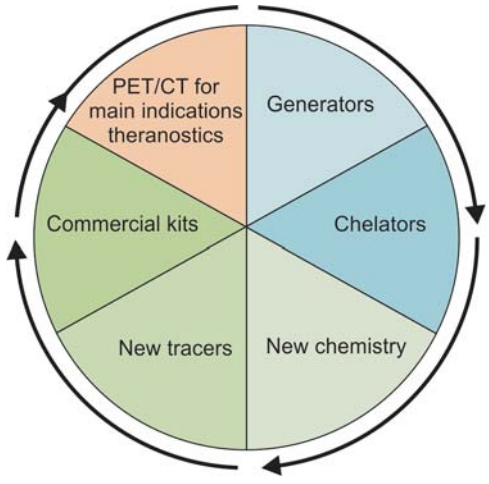

Fig. 7: Sketch of some future directions related to $^{68}Ge/^{68}Ga$ radionuclide generators and radiopharmaceuticals

technologies, ^{68}Ga radiopharmaceuticals are being synthesized routinely and safely. Thus, since the early $^{68}Ge/^{68}Ga$ radionuclide generator systems developed about half a century ago, significant advances have been made.

These generator improvements have allowed for the significant development of ^{68}Ga radiopharmaceutical chemistry within the last decade. Despite this, almost all the technological and chemical innovation involved belongs to the 20th century. There is room for further development, where several aspects of generator design and performance, labeling chemistry and clinical application need to be addressed. Figure 7 illustrates some of the potential future directions.

Generators

Concerning solid phase-based ion exchange chromatographic $^{68}Ge/^{68}Ga$ radionuclide generators, some improvements may be possible within the resin material itself. Recent publications hint at the potential of sophisticated nanoparticles, such as Zr^{IV} and Ce^{IV}-systems, which are classified as nanocomposites.[12,13] The rational is that these composites may provide effective adsorption of ^{68}Ge, effective release of ^{68}Ga, be more chemically stability and radiation resistant. In parallel, GMP-certified and licensed commercial generators are required to satisfy the increasing standards of legal authorities.

Generator Online Post-Processing

Elution of generators may be further integrated into faster and more efficient online post-processing procedures, which are managed by automated modules. A key issue in this regard, is to avoid the transfer of ^{68}Ge into ^{68}Ga-radiopharmaceuticals. Optionally, these post-processing technologies should also allow for versatile labeling protocols. For example, the transfer from aqueous to nonaqueous solutions for radiolabeling (addressing potential lipophilic ^{68}Ga tracers)[53] or onto resin for solid phase supported labeling reactions.

Post-processing technologies, which remove ^{68}Ge online from the eluate, are of utmost importance, as they avoid the transfer of critical ^{68}Ge levels into the radiopharmaceutical preparation. They also guarantee the safety, which is relevant from the legal point of view, i.e. addressing safety criteria of routine clinical use.[9] Although some of the ^{68}Ga radiopharmaceuticals used clinically, in particular ^{68}Ga-based peptides, are purified from uncomplexed ^{68}Ga, (which simultaneously removes ^{68}Ge present), the principal strategy should be to keep generator-derived ^{68}Ga solutions free of ^{68}Ge before labeling. Consequently, the monographs of the European Pharmacopoeia (Ph Eur) in its description of the gallium chloride (^{68}Ga) solution for radiolabeling, Monograph N°: 2464, Strasbourg, June 2012, adds, that '…the solution is intended for use in the preparation of gallium-68-labeled radiopharmaceuticals, including a procedure to reduce the level of germanium-68 below 0.001% of the total radioactivity.' This means that, necessarily, the procedure for preparation of a Ga-68 radiopharmaceutical has to include a procedure to remove germanium-68 up to a level below 0.001%.

Only this strategy will be suitable for a kit-type ^{68}Ga-labeling approach to parallel the ^{99m}Tc analog systems. This would allow for the direct synthesis and application of ^{68}Ga radiopharmaceuticals, such as ^{68}Ga chloride,[49] ^{68}Ga

citrate[28,37] (Rizello et al 2009), ^{68}Ga apotransferrin[27] or ^{68}Ga Schiff base complexes.[18,19] Radiotracers, such as these are otherwise not applicable due to the nonseparable content of ^{68}Ge.

Ligands

The future development of new ^{68}Ga radiopharmaceuticals may be facilitated by the development of new ligands and bifunctional derivatives for coordinating ^{68}Ga specifically, i.e. ideally discriminating Fe^{III} and Zn^{II}, or by allowing complex formation under a broader range of pH. Another relevant aspect is the development of ligands which complex ^{68}Ga at room temperature. Such radiolabeling characteristics approach the advantages of ^{99m}Tc kit-type labeling protocols. It is also desirable to speed up complex formation and minimize the amount of labeling precursor needed, thereby increasing the specific activities of the final radiolabeled product. Ideally new ligands should label more efficiently than that of established DOTA or NOTA derivatives, without detriment to complex stability. Important criteria (in addition to high radiochemical yields) are listed in Table 1. Several of the promising ligand candidates for ^{68}Ga radiolabeling are listed in Figure 8.

Current trends in bifunctional ligand design suggest a change in the paradigm that macrocyclic chelates are the ligands to go for. Recent developments describe modified acyclic ligands. In particular, recent ligands are derived from known Fe^{III} ligands, because the two metals have similar coordination chemistry. New classes of chelators currently under development, include acyclic ligands HBED,[14,48] H_2DEDPA[7,8,24] and tris(hydroxypyridinone) ligands,[6,53] but also research on deferoxamine[34] and on sulfur-based derivatives[30] continues.

New cyclic triazacyclononane-phosphinic acid chelators[38,39] have been developed, which complex ^{68}Ga very effectively. In case of the triazacyclononane-phosphinic acid chelators (TRAP), the idea is also to create an inert coordinating core leaving three linkable functionalities available for versatile chemistry, allowing for multimeric substitutions.

Table 1: Challenges for new ^{68}Ga ligand developments

Efficient labeling should occur:
- At temperatures below 100°, approaching room temperature
- Over a broad range of pH, i.e. covering the pH of the generator eluate up to physiological pH
- Within short periods, i.e. within 10 minutes or less
- At low amounts/concentration of the ligands (10 μM or less)
- In the presence of impurities, such as Fe^{III} (as a general impurity) and Zn^{II} (as decay product of ^{68}Ga), etc.

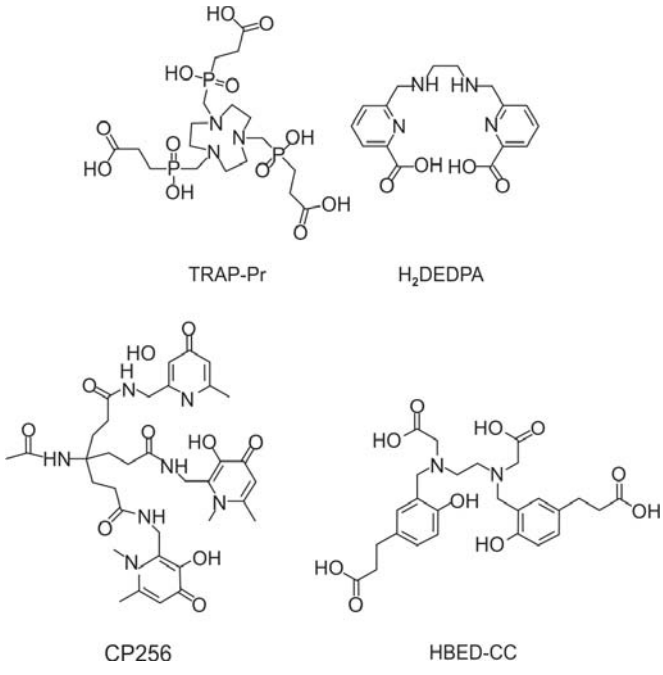

Fig. 8: Recent developments in ligand structures tailored for ^{68}Ga

^{68}Ga Radiopharmaceuticals

Novel ligand design presents the opportunity for a wide range of new tracers. The clinical application, however, will finally depend on the classes of targeting vectors attached, beyond peptidic and nonpeptidic targeting vectors available. Imaging will hopefully address tumors, infection and inflammation, but also a variety of clinical indications and almost all organs. This would mirror the ^{99m}Tc radiopharmaceuticals, e.g. brain, heart, etc. In the context of the similarity of generator based ^{99m}Tc and ^{68}Ga pharmaceuticals, the preparation of those ^{68}Ga radiopharmaceuticals should also be KIT-based if they are to find clinical application and widespread acceptance. These developments will contribute to a much more intense clinical use of ^{68}Ge/^{68}Ga generators and the corresponding ^{68}Ga pharmaceuticals for molecular imaging. Again, legal considerations apply to both the generator and the pharmaceuticals.[9]

Theranostics

Simultaneously to the further development of ^{68}Ga-PECT/CT diagnostics, it is one of the unique features of ^{68}Ga, that ^{68}Ga-PET/CT imaging may be directly linked to treatment options. For some classes of Ga^{III} bifunctional ligands, there should be an option to synthesize therapeutics analogs with trivalent radiometals, such as ^{90}Y, ^{177}Lu, ^{213}Bi, etc. The DOTA-conjugated octreotide derivatives represent a perfect example of the success of this theranostic concept.[42]

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