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Past, present and future of ^{68}Ge/^{68}Ga generators

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ABSTRACT

^{68}Ga represents one of the very early radionuclides applied to positron emission tomography (PET) imaging at a time when even the wording PET itself was not established. Today it faces a renaissance in terms 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). Thanks to the pioneering achievement of radiochemists in Obninsk, Russia, a new type of ^{68}Ge/^{68}Ga generators became commercially available in the first years of the 21st century. 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. Consequently, the last decade has seen a ^{68}Ga rush. Increasing applications of generator based ^{68}Ga radiopharmaceuticals (for diagnosis alone, but increasingly for treatment planning, thanks to the inherent option as expressed by THERANOSTICS, ask for new developments towards the optimisation of ^{68}Ge/^{68}Ga generators both from chemical and regulatory points of view.

1. Introduction

Gallium-68 today sees a renaissance in terms of new ^{68}Ge/^{68}Ga radionuclide generators, sophisticated ^{68}Ga radiopharmaceuticals, and state-of-the-art clincial diagnoses via PET/CT (Roesch and Riss, 2010). Why "renaissance"?

^{68}Ga represents one of the very early radionuclides applied to PET imaging at a time when even the wording PET itself was not established, long time before the usage of e.g. fluorine-18. Moreover, due to the availability of this positron emitter via the first ^{68}Ge/^{68}Ga generators (Gleason, 1960; Greene and Tucker, 1961; Yano and Anger, 1964), Hal Anger could create the first positron scintillation camera in the beginning of the 1960s.

Driven thus by the coincidence of old-fashioned radiochemistry and first-generation ^{68}Ge/^{68}Ga radionuclide generators available in the early 1960s, in particular those providing ^{68}Ga-ethylenediaminetetraacetic acid (Ga-) eluates, and dramatic improvements of tomographic detection systems, several ^{68}Ga tracers for imaging of various diseases were investigated, mainly for imaging the human brain. Hundreds of patients have been almost immediately investigated in the USA with ^{68}Ga-EDTA and others from 1963 onwards.

Although several publications described "improved"^{68}Ge/^{68}Ga radionuclide generators, the impact of ^{68}Ga imaging fated away in the late 1970s, because of mainly two reasons: the generator design itself appeared not adequate to the requirements of versatile syntheses of ^{68}Ga radiopharmaceuticals, and the ones available through the existing technology had minor clinical relevance, in particular in view of the parallel and rapid developments of the new classes of ^{99m}Tc- and ^{18}F-labelled diagnostics. Nevertheless, numerous 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.

Thanks to the pioneering achievement of radiochemists in Obninsk, Russia, a new type of ^{68}Ge/^{68}Ga generators became commercially available in the first years of the 21st century (Razbash et al., 2005). 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 (Me^{III}=trivalent metals). Again conicidently, the ^{68}Ga cation was introduced immediately into existing designs of MRI and single-photon emission computed tomography (SPECT) imaging probes, namely diethylenetriaminepentaacetic acid (DTPA)- or 1,4,7,10-tetraazacyclododecane–1,4,7,10-tetraacetic acid (DOTA)-based derivatives. The impressive success of utilising ^{68}Ga-DOTA-octreotides and PET/CT instead of e.g. ^{111}In-DTPA-octroescan paved the way not only to the clinical acceptance of this particular tracer for imaging neuroendocrine tumours, but also to the realisation of the great potential of the ^{68}Ge/^{68}Ga generator for modern nuclear medicine in general.

Consequently, the last decade (from 2000 onwards) has seen a ^{68}Ga rush. Increasing applications of generator based ^{68}Ga radiopharmaceuticals (for diagnosis alone, but increasingly for

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treatment planning thanks to the inherent option as expressed by THERANOSTICS) (Roesch and Baum, 2011), ask for progressive developments towards the optimisation of ^{68}Ge/^{68}Ga generators both from chemical and regulatory points of view. Dedicated chelators may be required to broaden the possibilities of ^{68}Ga labelling of more sensitive targeting vectors. Last but not least, the concept of ^{68}Ga-radiopharmaceutical chemistry should be applied to an increasing number of targeting vectors, addressing the clinically most relevant diseases.

It may be a vision, may be a dream: in another decade from now onwards, ^{68}Ge/^{68}Ga generator based ^{68}Ga diagnostics may approach rank 3 or 4 of clinical impact molecular imaging after that of ^{99m}Tc and ^{18}F and radioiodine based tracers.

2. The early years (1960–1970): the sunrise of ^{68}Ga

2.1. The first ^{68}Ge/^{68}Ga radionuclide generators

The first ^{68}Ge/^{68}Ga radionuclide generator was described in 1960 (Gleason, 1960): "A positron cow". The title immediatly delivers the message: which is applying the concept of a radionuclide generator to a positron emitting radionuclide. The latter itself was a new entry for radiopharmaceutical chemistry and nuclear medicine molecular imaging *in vivo*. The generator chemistry was liquid–liquid extraction, and the whole processing was by far not revealing the real features of todays radionuclide generator systems. Here are some key sentences from Gleasons paper:

"The Germanium-68 comes to us from the cyclotron in a solution buffered to pH 6.4. The accumulated gallium can be milked off every 3–4 h. A 35% solution of fresh acetyl–acteone in cyclohexane is mixed vigorously for 2 min with the germanium solution and yields on numerous tests a 70–80% recovery of available gallium in the solvent. The gallium is collected by mixing for 2 min with a solution of 0.1 N HCl. (1 mg of $GaCl_3$ is added to the germanium solution every three to four separations to insure adequate carrier for the very small amounts of radioactive gallium present) The gallium chloride is neutralised with normal sodium hydroxide, yielding a solution containing 1 mg or less of gallium chloride, containing 2–3 mCi of gallium-68. No germanium-68 is carried over under these circumstances."

Nevertheless, a variety of ^{68}Ga compounds have been synthesised, cf. Shealy et al., 1964:

> *Gallium versenate*: 10 mg of sodium versenate added to the extraction product and the mixture heated for 2 min. This is injected intravenously and scanning begun about 20 min later. We have not yet had sufficient quantity to start scans at 1 h which would be desirable.
> *Gallium protoporphyrin*: The neutralised gallium is added to 1 mgprotoporphyrin and heated for 5 min. The solution is injected intravenously and scanning begun 45–60 min later.
> *Gallium phthalocyanate*: The neutralised gallium chloride, $GaCl_3$, is added to 30 mg sodium phthalocyanate, and after heating for 1 min this is injected intravenously.
> "*Ionic*" *gallium*: The neutralised solution is injected intravenously and scanning is begun 30–60 min later.
> *Sodium gallate*: 1 N Sodium hydroxide is added to the neutral gallium to bring the solution to pH 9. This is injected intravenously, and scanning begins 30–60 min later.
> *Sodium galloarsenate*: Neutralised gallium chloride is added to 1 mg sodium arsenate in a strongly basic solution and autoclaved for 15 min.

In all these compounds an excess of chelating agent or of solution is present. Purer preparations might be more useful but have not been made yet.

2.2. Further generator developments: Al_2O_3-based EDTA-eluted generators

Because of these inherent disadvantages of the first generator, soon after, two improved generator concepts have been described. The liquid–liquid extraction chemistry introduced by Gleason was substituted by solid phase based ion exchange system (Greene and Tucker, 1961; Yano and Anger, 1964). (Nevertheless, an improved liquid–liquid extraction version was described in 1978 (Erhardt and Welch, 1978), cf. Fig. 1.

The concept of the solid phase based generator is illustrated in Fig. 2 and the original sketch is taken from the original publication by Yano and Anger (1964), cf. Fig. 3.

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 and repeatedly eluted in 95% yield without the need to introduce stable Ga^{III} as carrier. "Gallium 68, the daughter of 270-day germanium 68, is obtained by passing edetate solution through an alumina column upon which ^{68}Ge is placed. The edetate becomes labelled with the short half-life ^{68}Ga, while the ^{68}Ge remains on the column to be "milked" again. Sterility is insured by using a suitable eluting solution and sterilising the eluent with a Millipore filter" (Yano and Anger, 1964).

The eluate contained as less as $< 1.4 \times 010^{-5}$% of the parent ^{68}Ge. Prior injections, 0.5 ml of 18% NaCl solution were added to the eluate. This system served as a convenient and economical source of ^{68}Ga-EDTA. Indeed, nuclear medicine physicians such as Gottschalk and others made extensive use of this tracer.

In a way, this radionuclide generator was basically a synthesis unit of a relevant radiopharmaceutical, ^{68}Ga-EDTA (named "veronate" these years).

2.3. ^{68}Ga-EDTA: the PET-pharmaceutical and development of positron scintillation cameras

Around 1960, "radioisotopic brain scanning" has been evaluated with a number of agents. Among the most satisfactory have been the positron emitters arsenic-74 (as arsenate), copper-64 (as versenate), and mercury-203 (as neohydrin).

In this context, Shealy et al. (1964) concluded the following: "Unfortunately these preparations present some technical difficulties and have not achieved widespread use. In searching for another positron-emitter, it is necessary to find one which for use with present equipment has a half-life of at least 1 h, but has a biological half-life of not more than a few days. Further, it should be readily obtainable and incorporable into a chemical form of high specific uptake and of low toxicity. Such an element is gallium-68 with a half-life of 66 min. It is particularly useful because it emits 85% positrons with few non-annihilation gammas. It is a natural decay product of germanium-68, which has a half-life of 250 days. Such a continuous and relatively inexpensive supply of isotope is desirable if the scanning test is to become widely used. A short-lived isotope such as Ga88 is of particular interest for use with camera-type detection systems. These show promise of reducing scanning time from the present hours to minutes".

^{68}Ga-EDTA and in rather few cases some more ^{68}Ga-tracers have been adapted for human application quite fast by various groups in the US. (EDTA itself and its relation to Ca^{II} were established well known to be non-toxic.) For early applications cf. e.g. Gottschalk and Anger, 1964; Schaer et al. 1965. Systematic application for brain imaging was reported, with medical impact seriously depending on the type of imaging applied. Conventional imaging appeared to be relatively difficult and relatively high activities of ^{68}Ga-EDTA were needed for valuable medical information. A typical scan of these years is illustrated in Fig. 4.

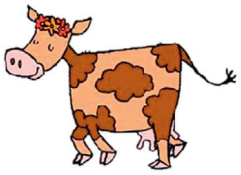
Gleason 1960		A positron cow
Greene and Tucker 1964		An improved gallium-68 cow
Yano and Anger 1964		A gallium-68 positron cow for medical use.

Fig. 1. Progress in $^{68}Ge/^{68}Ga$ radionuclide generators I: design of cows towards medicine.

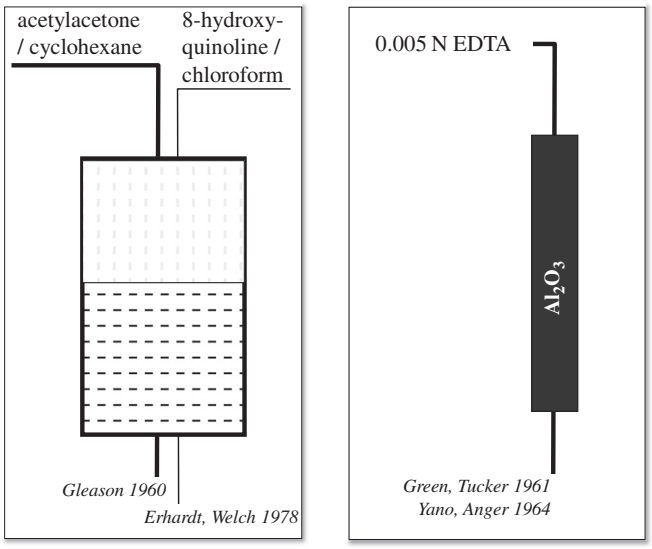


Fig. 2. Progress in $^{68}Ge/^{68}Ga$ radionuclide generators II: from liquid–liquid extraction to solid phase-based elution.

Anger thus started to develop the basics of positron imaging tomography (cf. e.g. Anger and Gottschalk, 1963; Gottschalk 1996, 2004), 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 Ga68 EDTA will detect lesions half 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 obtained in 4–10 min with a dose of 350–750 mci of Ga68-EDTA. Shealy et al., however, found that 2–3 mCi of Ga68-EDTA was sometimes an inadequate dose with their positron scanner" Fig. 5.

Despite of these new features and the great success of ^{68}Ga-EDTA molecular imaging, there was an obvious limitation of the generator application, as it was in practice limited to the synthesis of

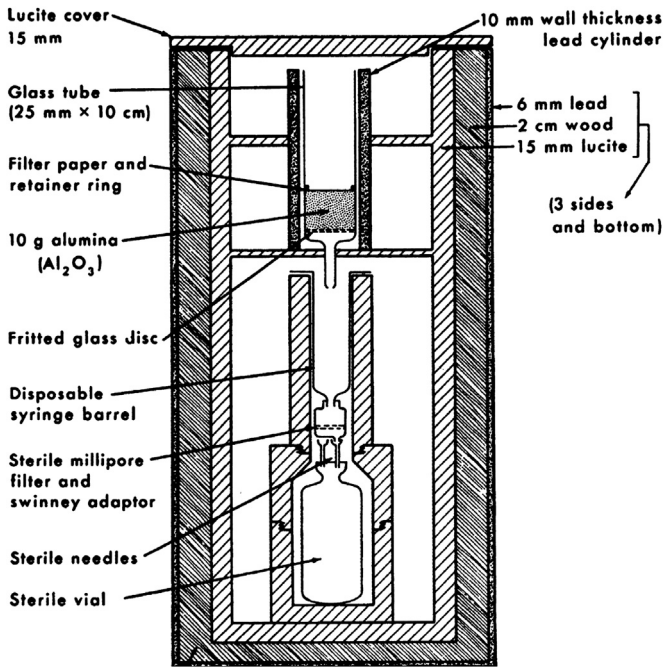


Fig. 3. Solid phase based (alumina) elution (by EDTA solution) taken from the original publication by Yano and Anger (1964).

^{68}Ga-EDTA exclusively. The transfer of ^{68}Ga out of the thermodynamically very stable (logK=21.7) eluate species ^{68}Ga-EDTA was not straightforward. Yano and Anger 1964 report, that: "attempts are being made to freed ^{68}Ga from the EDTA complex". The procedure, however, was by far not user friendly. The time required was given with 30 min, and the transfer yield at 10 mg Ga carrier was 60% (Yano and Anger 1964). The protocol was as follows:

(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) 10–20 mg of carrier $GaCl_3$ in HCl solution is added. (3) The 0.5 ml of saturated ammonium acetate solution is added. (4) Concentrated

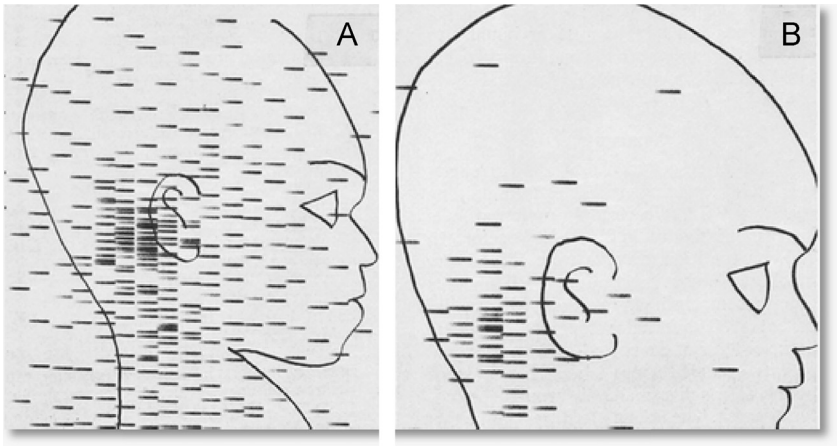


Fig. 4. Cisternal blockade in an infant with posterior spread of a glioma of the optic chiasm. 500 μc of ^{68}Ga were given via the lumbar route. In the first scan (Scan A), an early rise to the cerebellar cisterns is found. Later scans, including Scan B, showed that the isotope remained in the posterior fossa and did not pass upward (McQueen and Abbassioun, 1968).

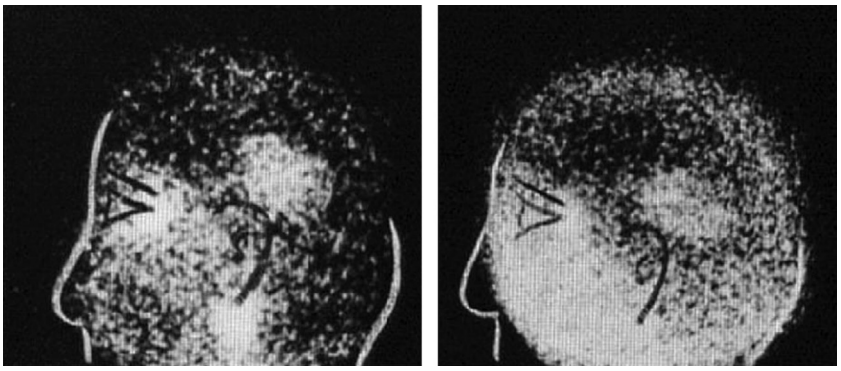


Fig. 5. A ^{68}Ga-EDTA brain scan acquired with the Anger positron camera circa 1962, showing the tomographic capability. The brain tumour is in best focus in the left image, taken at about the level of the temporal horn (Anger and Gottschalk, 1963).

NH_4OH is added drop wise (about 1 ml) to precipitate $Ga(OH)_3$ at pH 6.0. (5) The solution is heated in a boiling water bath for 10 min 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.

3. Hibernating ^{68}Ga medical applications, but new chemistry ahead

The impact of ^{68}Ga imaging started to fate away in the late 1970s, because of mainly two reasons: the generator design itself appeared not adequate to the requirements of versatile syntheses of ^{68}Ga radiopharmaceuticals, and the ones available through the existing technology had minor clinical relevance, in particular in view of the parallel and rapid developments of the new classes of ^{99m}Tc- and ^{18}F-labelled diagnostics.

The same time, however, 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.

In fact, the chalange was to design radiochemical separation systems to provide cationic ^{68}Ga eluate species available for versatile radiolabelling chemistry. Ga^{III} exists as cationic species (either pure water-hydrated aquo-complexes such as the hexaaqua cation $Ga(H_2O)_6^{3+}$, or similare mono-chloro or mono-hydroxo species). This speciation is easily achieved in solutions of hydrochloric acid of pH ranging between 0 and 2, approximately (i.e., 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, effectively adsorbing $^{68}Ge^{IV}$, e.g. Kopecky et al. 1973, 1974; Malyshev and Smirnov, 1975; Loch et al., 1980; Ambe, 1988. Alternatively, organic resins have been developed eluting ^{68}Ga in more stronger HCl, e.g. Arino et al., 1978; Neirinckx and Davis, 1980; Schumacher and Maier-Borst, 1981, the latter using pyrogallol–formaldehyde modified columns (Fig. 6).

4. Commercial "ionic" generators

4.1. Generator eluates delivering the gallium cation

Thanks to the pioneering achievement of radiochemists in Obninsk, Russian Federation, a new type of ^{68}Ge/Ga generators became commercially available in the first years of the 21st century (Razbash et al., 2005). 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 (Fig. 7).

Again conicidentally, the ^{68}Ga cation was introduced immediately into existing designs of MRI and SPECT imaging probes, namely DTPA- or DOTA-based derivatives. The impressive success of utilising ^{68}Ga-DOTA-octreotides and PET/CT instead of e.g. ^{111}In-DTPA-octroescan paved the way not only to the clinical acceptance of this particular tracer for imaging neuroendocrine tumours, but to the realisation of the great potential of the ^{68}Ge/^{68}Ga generator for modern nuclear medicine in general.

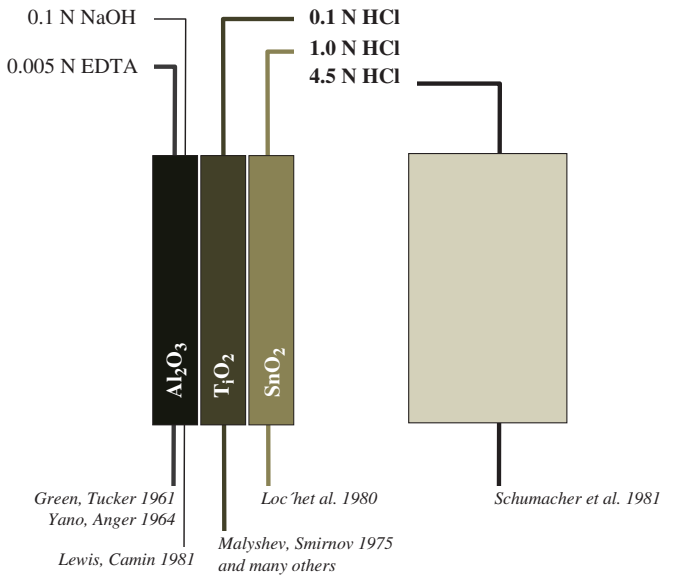


Fig. 6. ^{68}Ge/^{68}Ga radionuclide generator concepts developed in the 1970s and 1980s towards "cationic" generators.

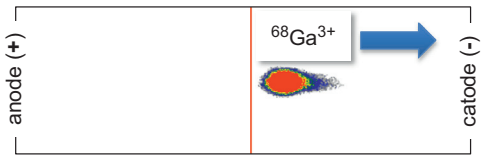


Fig. 7. Electrophoresis of a 0.1 N HCl ^{68}Ga generator eluate (EZAG Obninsk generator; EZAG=Eckert & Ziegler Strahlen- und Medizintechnik AG) demonstrating the presence of "cationic" ^{68}Ga. (parameters: 0.1 N HCl, Whatman paper strip, l=19 cm, t=5 min, 191 V, 210 mA, 40 W).

While commercial "ionic" generators thus entered clinical environments, questions on the adequate use concerning radiation safety, legal requirements and labelling of medical tracers became more and more relevant.

Problem 1. The long physical half-life of the parent in principle should allow usages of at least one year. However, the shelf-life of the generators did not necessarily parallel this long physical half-life due to decreasing qualities of the generator itself in terms of ^{68}Ga elution yield, but mainly due to increasing breakthrough of ^{68}Ga. ^{68}Ge breakthrough reduction and/or removal of ^{68}Ge from the eluate thus is an important radiochemical challenge.

Problem 2. ^{68}Ga generator eluates are not chemically pure and radionuclidic pure either. No-radioactive 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 may represent metals competing with ^{68}Ga^{III} for coordinative labelling of radiopharmaceutical precursors. Again, removal of ^{68}Ge from the eluate thus is another important radiochemical challenge (Zhernosekov et al. 2007).

Problem 3. The new generation of ^{68}Ge/^{68}Ga radionuclide generators utilises hydrochloric acid solutions for ^{68}Ga elution. The relatively high concentration of H^+ may protonate functional groups of ligands and bifunctional ligands needed for the labelling of ^{68}Ga. Finally, minimising the pH and volume of ^{68}Ga eluted prior to labelling should facilitate syntheses yields.

4.2. Generator post-processing

In this context, 3 approaches have been developed to address one or more of these problems. Two processes include chemical separation strategies and may be called post-processing", while a third technology is simple fractionation of the eluate, i.e. isolating eluate fractions with highest ^{68}Ga concentration. The 3 methods are schematically illustrated in Fig. 8.

In most cases, these generators are being used in direct connexion with one of the three post-eluate processing technologies mentioned. In particular the cation exchange-based post-processing guarantees almost complete removal of the metallic impurities, in particular ^{68}Ge. It thus avoids the transfer of critical ^{68}Ge levels into the radiopharmaceutical preparation and guarantees a save use of the systems, which is upmost relevant from the legal point of view, i.e. addressing safety criteria of routine clinical use.

5. Current state/outlook

5.1. Generators

Today, ^{68}Ge/^{68}Ga radionuclide generators are commercially available, either TiO_2- or SnO_2-based or using an organic resin. ^{68}Ga eluate yields range from about 70% to 80% for fresh generators, with more or less pronounced decrease over time. ^{68}Ge breakthrough is at levels of about 0.01–0.001% or even better for fresh generators, with increasing percentages over longer periods of generator usage. Conjugated with post-processing technologies, ^{68}Ga radiopharmaceuticals are being synthesised routinely and safely. Thus, times have been a-changin´ since the early ^{68}Ge/^{68}Ga radionuclide generator systems, developed about half a century ago. (Interestingly, times have been a-changing for nuclear decay data of both generator parent and daughter. Fig. 9 schematically compares "old" and current values for half-life and positron branching (Burrows, 2002; Schönfeld, 1999). Most recent numbers are $T½$=270.95 days for ^{68}Ge and $T½$=67.71 min for ^{68}Ga, with an 89.14% positron branching of ^{68}Ga.

5.2. Future developments

Times have been a-changin´ thus significantly within the last decade. Nevertheless, almost all the technology and chemistry involved belongs to the 20th century. Definitely, there is a room for further development addressing several aspects of generator design and performance, labelling chemistry and clinical application. Fig. 10 illustrates some of future directions.

Concerning solid phase based ion exchange chromatographic ^{68}Ge/^{68}Ga radionuclide generators, some improvements may be within the resin material itself, in order to decrease the release of ^{68}Ge over time of generator usage. Recent publications hint on the potential of sophisticated nanoparticles, such as Zr^{IV} and Ce^{IV}-systems, classified as nano-composites (Chakravarty et al., 2010, 2011). The rational is to guarantee for effective adsorption of ^{68}Ge, effective release of ^{68}Ga, chemical stability and radiation resistance.

In parallel, good manufacturing practice (GMP)-certified and licensed commercial generators are needed to satisfy the increasing requirements by legal authorities.

Elution of generators may further be integrated into improved online and fast and efficient post-processing procedures managed by automated modules. A key issue is to avoid the transfer of ^{68}Ge into ^{68}Ga-radiopharmaceuticals. Optionally, these post-processing technologies should allow for versatile labelling protocols, including e.g. the transfer from aqueous to non-aqueous solutions (addressing

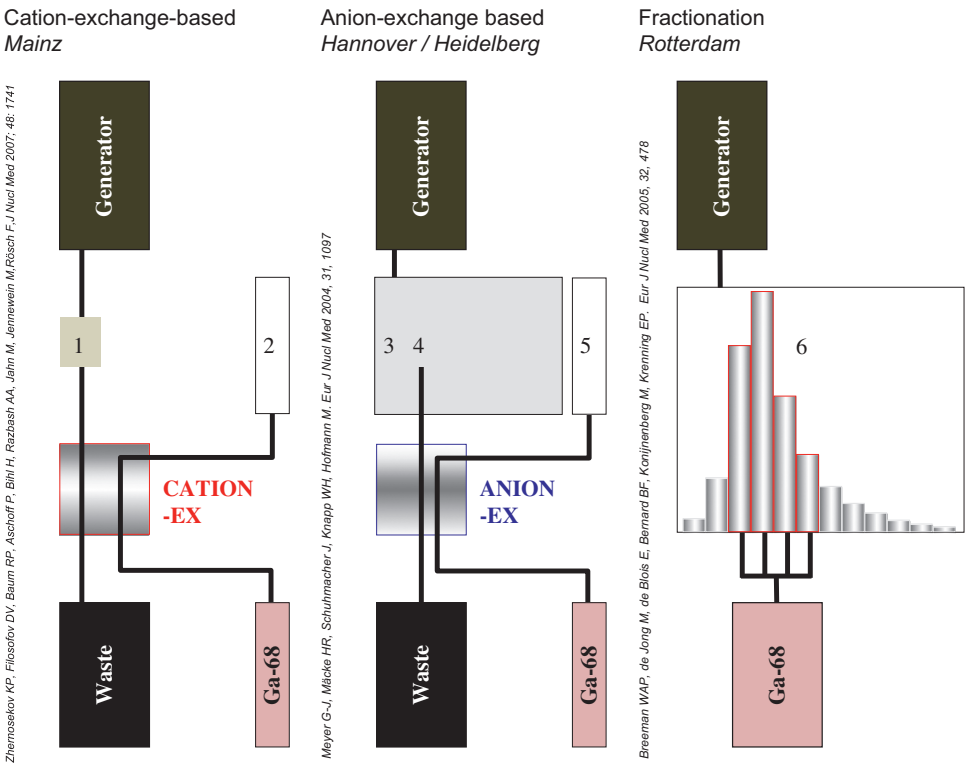


Fig. 8. Overview on post-processing technologies for commercial $^{68}Ge/^{68}Ga$ radionuclide generators. (1): Direct generator elution through cation-exchange cartridge, (2): desorption of purified ^{68}Ga using HCl/acetone or HCl/ethanol mixtures, (3): generator elution into HCl reservoir, (4): subsequently elution through anion-exchange cartridge, (5): desorption of purified ^{68}Ga using water, (6): identification of the eluate fraction representing at least 2/3 of the ^{68}Ga activity and use without further purification.

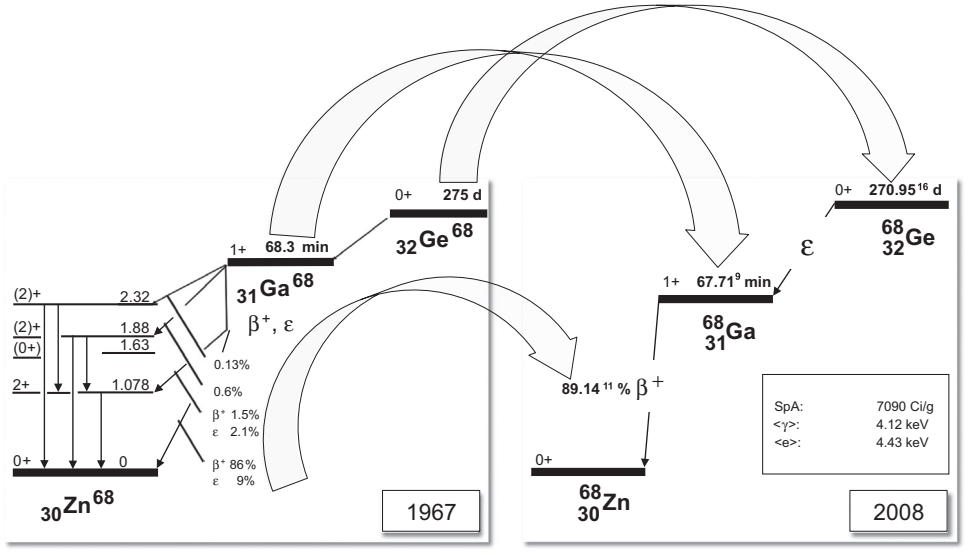


Fig. 9. Nuclear decay parameters of the $^{68}Ge/^{68}Ga$ chain from 1967 and from 2008.

potential lipophilic ^{68}Ga tracers) (Zoller et al., 2010) or on-resin, solid phase supported labelling reactions.

$^{68}Ge/^{68}Ga$ radionuclide generator performances may be facilitated by developing new ligands and bifunctional ligands 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. In fact, new classes of chelators are under development, such as acyclic ligands HBED (Sun et al., 1996; Eder et al., 2008); H_2DEDPA (Koop et al., 2007), tris(hydroxypyridinone) ligands (Zhou et al., 2006; Berry et al., 2011) or cyclic triazacyclononane-phosphinic acid chelators (Notni et al., 2010, 2011); (HBED=N,N-bis(2-hydroxybenzyl)ethylenediamine-N,N-diacetic acid, H_2DEDPA=1,2-[{6-(carboxylato-)pyridin-2-yl}methylamino]ethane). The rational here is to allow for instant labelling at convenient temperatures, to provide high thermodynamic and kinetic Ga^{III}-ligand-complex stability. Ideally, new types of Ga^{III} chelate ligands may discriminate between Ga^{III} and Fe^{III} and other competing metals. In case of the triazacyclononane-phosphinic acid chelators (TRAP) the idea is to create an inert coordinating core leaving 3 linkable functionalities available for versatile chemistry.

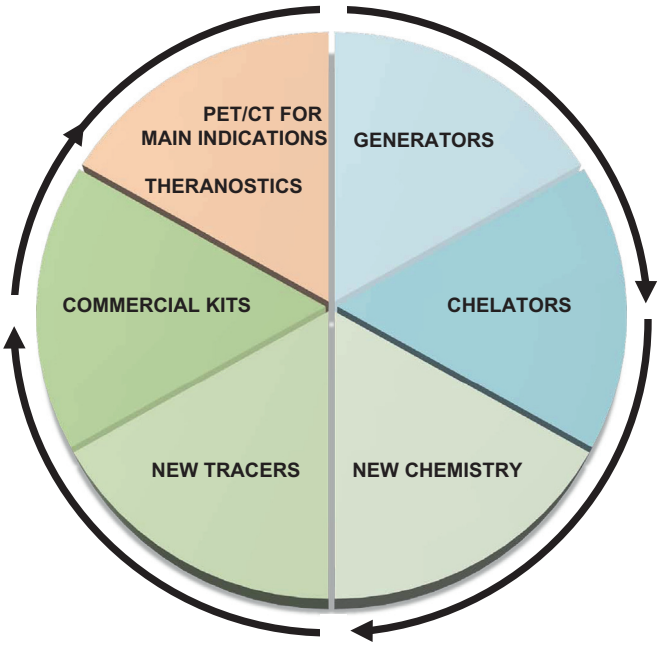


Fig. 10. Sketch of some future directions related to ^{68}Ge/^{68}Ga radionuclide generators.

New generators of ligands may open access to new monomeric derivatives (one bifunctional chelate conjugated to one molecular targeting vector), but also to di-, tri- and multi-meric analogues. The one central chelate core thus will become a biologically almost inert unit, linked to one or several active targeting moieties.

New tracers thus are ahead representing new ligand and coordination chemistry. The clinical application, however, will finally depend on the classes of peptidic and non-peptidic targeting vectors available. Imaging will hopefully address not only tumours, but may cover a variety of clinical indications similar to the ^{99m}Tc radiopharmaceuticals: brain, heart etc.

In the context of the similarity of generator based ^{99m}Tc and ^{68}Ga pharmaceuticals, there may be a challenge to develop KIT-type systems also for ^{68}Ga.

These developments finally will contribute to a much more intense clinical use of ^{68}Ge/^{68}Ga generators and the corresponding ^{68}Ga pharmaceuticals for molecular imaging. However, it is one of the unique features of ^{68}Ga, that ^{68}Ga-PET/CT imaging is directly linked to treatment options. For some classes of GaIII bifunctional ligands, the option to synthesise therapeutics analogues with trivalent radiometals such as ^{90}Y, ^{177}Lu, ^{213}Bi etc. represents a perfect example of the theranostic concept (Roesch and Baum, 2011).

With the existing state-of-the-art ^{68}Ge/^{68}Ga radionuclide generators and post-processing technologies, and thanks to the exciting ^{68}Ga radiopharmaceuticals available and under dvelopment, in another decade from now on, ^{68}Ge/^{68}Ga generator based ^{68}Ga diagnostics may approach a clinical impact in molecular imaging closer to ^{99m}Tc and ^{18}F and radioiodine based tracers.

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