Development of Novel Radionuclide Generators for Use in Nuclear Medicine

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Introduction
Over the last 5 decades, radionuclide generators have attracted substantial attention, indeed close scrutiny of the nuclear medicine community owing to their ability to provide short-lived radioisotopes without the need for on-site nuclear reactor or cyclotron facilities for preparation of a wide variety of diagnostic and therapeutic radiopharmaceuticals [1]. The radionuclide generators not only provide no-carrier-added (NCA) radionuclides on-demand basis, but also in a cost-effective way where the payoff of benefits is substantial and invaluable [1]. Nuclear medicine and radionuclide generator feed off of one another, thereby, propelling both forward. Utility of radionuclide generators has virtually pervaded most areas in the field of nuclear medicine and their importance has been well demonstrated and recognized [1].

The current importance and success of diagnostic imaging in nuclear medicine is primarily due to $^{99m}$Tc generator [1]. A large number of the nuclear medicine procedures in remote areas far from the site of a cyclotron or reactor facility would not have been possible but for the availability of this radionuclide generator [1]. It would not be an exaggeration to state that the field of nuclear medicine owes its existence to the development of this generator in 1957 at Brookhaven National Laboratory in United States [1]. The subsequent years have seen an enormous increase in the use of generators such as $^{90}$Sr/$^{90m}$Y and $^{188}$Re/$^{188}$W generators to provide therapeutic radionuclides, which has paralleled the development of complementary strategies for targeted radiotherapy [2-4]. With the recent advances in clinical positron emission tomography (PET), use of the $^{68}$Ge/$^{68}$Ga generator is showing enormous potential as a source of positron-emitting $^{68}$Ga which can be used for preparation of a wide variety of radiopharmaceuticals [5, 6].

Basic Concept of Radionuclide Generator
A radionuclide generator is a self-contained system housing an equilibrium mixture of a parent/daughter radionuclide pair [1]. The system is designed to separate the daughter radionuclide formed by the decay of a parent radionuclide by virtue of their differences in chemical properties [1]. The parent-daughter nuclear relationships offer the possibility to separate the daughter radionuclide at suitable time intervals.

Emerging Concepts in Radionuclide Generator Technology
A separation science is subject to continuous evolution, any revolutionary breakthrough in this subject represents not only an important driving force, but also lays the cornerstone towards the development of new radionuclide generators [7]. With the emergence of professionally run centralized radiopharmacies, the use of radionuclide generator technology is pointing to an era of a paradigmatic shift from the present designs and user profiles. In order to sustain the nuclear medicine service using generator derived radionuclides, it is of utmost importance to nurture emerging separation technologies in an appropriate manner, both in absolute, as well as in relative, terms of missions, goals, and requirements, to respond to the foreseeable changes in radionuclide generator technology.

In the recent times, our group has introduced two new concepts in the field of radionuclide generators, which are poised to bring paradigm shift in nuclear medicine practices in the foreseeable future. While the first approach involves the use of electrochemical separation technique [8, 9], the second involves the use of sorbents based on nanomaterials for use as column chromatography matrices [10] for the preparation of radionuclide generators.

Electrochemical Separation
Electrochemical method provides a simple and convenient approach of performing a wide variety of metal ion separations. A mixture of metal ions having adequate difference in their formal potential values in an electrolytic medium can be mutually separated by selective electrodeposition of one metal on an electrode surface under the influence of controlled applied potential (Fig. 1). In-situ electrodeposition of a daughter radionuclide is an attractive route to develop radionuclide generators. The major advantage of this approach is that the daughter radioisotope can be obtained with very high radionuclidic purity and radioactive concentration, irrespective of the specific activity of the parent radioisotope. This approach has been used for development of a variety of radionuclide generators, such as, $^{90}$Sr/$^{90m}$Y, $^{99m}$Tc and $^{188}$Re generators [8].
Column Chromatography using Nanosorbents

The second approach is based on the use of nanomaterials based sorbents as column matrices for the preparation of radionuclide generators (Fig. 2) relies on the unique morphological features, pore structure, high surface areas and high surface charge of nanomaterials [1, 10]. Such sorbents demonstrate much higher sorption capacity and selectivity for sorption of the parent radioisotope compared to their bulk counterparts. The daughter activity can be obtained with appreciably high radioactive concentration and purity suitable for biomedical applications. Over the last 10 years, a wide variety of nanostructured metal oxides such as polymer embedded nanocrystalline titania (TiP), mixed phase nanocrystalline zirconia (nano-ZrO₂), tetragonal nanozirconia (t-ZrO₂), nanocrystalline γ-alumina (γ-Al₂O₃), mesoporous alumina (MA) and nanoceria-polyacrylonitrile (CeO₂-PAN) composite have been synthesized by our group for preparation of ⁹⁹Mo/⁹⁹ᵐTc, ¹⁸⁸W/¹⁸⁸Re and ⁶⁸Ge/⁶⁸Ga generators (Fig. 3) [10]. It is pertinent to point out that in case of all the nanosorbents used for preparation of radionuclide generators, the synthesis methods adopted were neither cumbersome nor used expensive precursors and was amenable for scale-up. All these nanomaterials exhibited good mechanical strength, granular properties and were amenable for column operations. However, all these sorbents consisted of agglomerated nanoparticles (Fig. 3). Agglomeration to a certain extent is essential for use of such materials as sorbent matrices in chromatographic columns. Very fine particles without agglomeration are not suitable for column chromatographic application as such materials are impervious to the flow of liquid through the column bed.

Fig. 1: Schematic diagram of electrochemical radionuclide generator

Fig. 2: Radionuclide generator based on column chromatographic separation. (A) Schematic diagram of a column chromatography generator housed in a lead shielded container to provide daughter radionuclide. (B) Schematic diagram of a chromatography column of a radionuclide generator.
The following sub sections provide an overview of the clinically useful radionuclide generators developed using the novel separation chemistry approaches described above.

**99Mo** for **99mTc** generator

Over the last 5 decades, a variety of **99Mo**/**99mTc** generator systems have been thoroughly investigated all over the world due to the everlasting demand for **99mTc**, which is the most commonly used medical radioisotope [1, 3]. This radioisotope is considered as the ‘workhorse’ of diagnostic nuclear medicine and is used for approximately 20–25 million procedures annually, comprising ~80% of all diagnostic nuclear medicine procedures. The column chromatographic **99mTc**/**99Mo** generator using a bed of acidic alumina has emerged as the most popular choice for producing **99mTc** in nuclear medicine departments worldwide [3]. However, the capacity of bulk alumina for taking up molybdate ions is limited (2–20 mg Mo per gram of alumina), necessitating the use of NCA **99Mo** produced through fission route [3]. Owing to the inherent complexities in production of fission **99Mo** and the vulnerability of irradiation services from 5 old research reactors which are currently in use for production of **99Mo**, there is an increasing consensus to use low specific activity **99Mo** for preparation of clinically useful **99Mo**/**99mTc** generators [3, 11]. However, the specific activity of **99Mo** is at least 1000-fold lesser than that of fission **99Mo** and is therefore not suitable for preparation of bulk alumina based column chromatographic generators [3].

In order to reduce reliance on fission **99Mo**, our group demonstrated for the first time the utility of electrochemical separation approach for preparation of clinical scale **99Mo**/**99mTc** generator [12]. This is primarily based on the selective electrodeposition of **99mTc** on a platinum electrode by taking advantage of the difference in formal electrode potentials of MoO₄²⁻ and TcO₄⁻ ions in alkaline media. The preferential electrodeposition of **99mTc** relies on applying a potential of 5 V in 0.1 M NaOH medium for 45 min. With a view to recover the **99mTc** deposit on the cathode, electrolysis was carried out in saline solution by reversing the polarity of the electrode and application of a high positive potential for a few seconds. In this process, the **99mTc** deposit could be quantitatively brought into saline solution, wherein **99mTc** existed as **99mTcO₄⁻**. It was demonstrated that the process was suitable for the separation of clinically useful **99mTc**, even from very low specific activity (~1.85 GBq/mg) **99Mo**.

Our group also demonstrated for the first time, the utility of nanosorbents such as TiP, t-ZrO₂, γ-Al₂O₃ and MA for preparation of clinical scale **99Mo**/**99mTc** generators [10, 13-15]. Recently, a comparative evaluation of the performance of the different nanosorbents reported was carried out to identify the best choice for preparation of **99Mo**/**99mTc** generators using (n,•)**99Mo** [16]. Though, **99Mo**/**99mTc** generators prepared using any of the nanosorbents met the requirements for use in preparation of radiopharmaceuticals, MA and •Al₂O₃ were identified as the best choices in view of their higher sorption capacities (~160 mg Mo/g) which could be used for preparation of clinical-scale **99Mo**/**99mTc** generator even while using (n,•)**99Mo** produced in medium flux reactors.

The performances of the **99Mo**/**99mTc** generators prepared by both the approaches remained consistent over a period of 2 weeks, which is comparable to the shelf life of the commercially available (fission **99Mo** based) **99mTc**/**99Mo** generators. Technetium-99m could be obtained with >99.99 % radionuclidic purity and the compatibility of the product in the preparation of **99mTc**-labeled formulations was found to be satisfactory.

**68Ge**/**68Ga** generator

The **68Ge**/**68Ga** generator is an excellent source for availing **68Ga** (**t₁/₂** = 68 min), which is a positron emitter, with 89% positron branching accompanied by low photon emission (1,077 keV, 3.22%) [1, 5]. The cyclotron-independent availability of **68Ga** from this generator in an ionic form has led to the development of a wide variety of **68Ga**-based radiopharmaceuticals, which have opened new horizons for molecular diagnostics using PET. Despite excellent attributes of **68Ga**-radiopharmacy, the low radioactive concentration, high acidity, unacceptable **68Ge** breakthrough, and the presence of potential metal ion impurities in the generator eluate have emerged as the major deterre
of increased $^{68}$Ge breakthrough and reduced $^{68}$Ga elution yield on repeated elutions over a prolonged period of time [5]. These limitations could be circumvented with the availability of ‘state-of-the-art’ automated modules for post-elution processing of $^{68}$Ga eluate and subsequent radiopharmaceutical preparation [5]. However, these automated modules are highly expensive and increases the production cost of $^{68}$Ga-based radiopharmaceuticals.

The development of $^{68}$Ge/$^{68}$Ga generators which could directly be used for preparation of radiopharmaceuticals without the need for post-elution processing of $^{68}$Ga was first reported by our group. CeO$_2$-PAN and t-ZrO$_2$ were used as sorbent matrices in these generators [6, 17]. Gallium-68 could be regularly eluted from these generators with $>$ 70% elution yield with high radionuclidic purity ($< 1 \times 10^{-5}$ % of $^{68}$Ge impurity), chemical purity ($< 0.1$ ppm of Ce, Ti, Ni, Fe and Mn ions) and was directly amenable for the preparation of $^{68}$Ga-labeled radiopharmaceuticals. The performances of the generators were evaluated for a period of 1 year. The generators gave consistent performance with respect to the elution yield and purity of $^{68}$Ga throughout the period of investigation. The CeO$_2$-PAN based $^{68}$Ge/$^{68}$Ga generator (named as ‘BARC’ $^{68}$Ge/$^{68}$Ga generator) was deployed in Tata Memorial Hospital (TMH), Mumbai (Fig. 4), where it was successfully used for preparation of clinically relevant doses of $^{68}$Ga-based radiopharmaceuticals for cancer diagnosis using PET.

90Sr/90Y generator

Yttrium-90 is a therapeutic radioisotope of enormous interest and radiopharmaceuticals based on $^{90}$Y are widely used for the treatment of cancer as well as in radiation synoviorthesis [4]. The broad interest in the use of $^{90}$Y in therapeutic nuclear medicine is due to its suitable nuclear characteristics ($t_{1/2} = 64.1$ h, $E_{\text{max}} = 2.28$ MeV, no - emission) and $Y^{3+}$ coordination chemistry suitable for complexation with various ligands and biomolecules. A radionuclide generator system based on the secular equilibrium of $^{90}$Sr decaying to $^{90}$Y is a convenient method for the production of high specific activity $^{90}$Y [4].

Over the past three decades, several separation techniques were reported for the development of $^{90}$Sr/$^{90}$Y generators [4]. Most of these separation techniques involve multiple steps employing conventional separation approaches such as solvent extraction, ion exchange or extraction chromatography either alone or in combination. However, none of these procedures are amenable for regular use in a hospital radiopharmacy or in a centralized radiochemistry laboratory because the level of $^{90}$Sr impurity in $^{90}$Y obtained from these systems does not meet the requirements prescribed in the pharmacopoeias for clinical use [4]. In view of the necessity to achieve a satisfactory degree of separation of $^{90}$Y from $^{90}$Sr, resorting to an electrochemical separation procedure was found to be effective [18]. The separation of $Y$ from a mixture of $Sr$ and $Y$ is based on the selective electrodeposition of $Y$ on a platinum electrode attributed to the difference in formal electrode potential of $Sr^{2+}$ and $Y^{3+}$ ions in acidic media. This enabled extraordinarily high decontamination factors ($^{90}$Sr/$^{90}$Y activity ratio $< 10^{-5}$) to be achieved and $^{90}$Y was obtained in a form suitable for preparation of radiopharmaceuticals. Adopting the process chemistry developed by our group, a fully automated electrochemical module for the electrochemical $^{90}$Sr/$^{90}$Y generator (named as ‘Kamadhenu’) was developed (Fig. 5) and is commercially available from Isotope Technologies Dresden (ITD), Germany. The automated module is already in operation in some countries. The above module is designed for the production of up to 37 GBq (1 Ci) of $^{90}$Y per day.
The $^{188}$W/$^{188}$Re generator is an excellent source for availing NCA grade $^{188}$Re, which has immense potential for use in therapeutic nuclear medicine [2, 19]. The preeminence of this radioisotope is primarily due to its excellent nuclear decay characteristics (reasonable half-life (16.9 h), high-energy beta radiation ($E_{\text{max}} = 2.118$ MeV), 155 keV (15.8% abundance) suitable for scintigraphic imaging and dosimetry) and convenient on-site availability from $^{188}$W/$^{188}$Re generators [2]. The chemistry of Re is similar to that of Tc since they belong to the same group in the periodic table, and this is an additional advantage towards preparing therapeutic analogues with molecules that have shown promising results in diagnosis as $^{99m}$Tc-radiopharmaceuticals. Most of the separation methodologies which have been reported for $^{99m}$Mo/$^{99}$mTc generators have also been exploited for preparation of $^{188}$W/$^{188}$Re generators [2]. Out of these procedures, the alumina based column chromatographic approach wherein $^{188}$W is absorbed on bulk alumina matrix and $^{188}$Re is selectively eluted using saline solution at regular intervals, has been identified as the most reliable method for the preparation of $^{188}$W/$^{188}$Re generator [19]. Owing to the limited sorption capacity of bulk alumina (~50 mg W/g), clinical-scale $^{188}$W/$^{188}$Re generator can only be prepared using high specific activity (150-190 GBq/g) $^{188}$W that can be produced in only few high flux ($\sim 10^{15}$ n.cm$^{-2}$.s$^{-1}$) reactors available in the world [2]. Even while using high specific activity $^{188}$W produced in these reactors, the $^{188}$W/$^{188}$Re generators currently available yield low specific volume (activity/mL) of $^{188}$Re and require post-elution concentration procedures prior to radiopharmaceutical preparation which is not always very convenient to perform in hospital radiopharmacies [2]. From this perspective, it is desirable to develop $^{188}$W/$^{188}$Re generators where the concentration step can be avoided to simplify the operational procedure for their widespread clinical utility.

Our group has exploited the utility of electrochemical separation approach for preparation of $^{188}$W/$^{188}$Re generator [20]. Electrolysis was carried out in oxalic acid medium by applying a potential of 7 V for 45 min, using platinum electrodes. The presence of oxalate ions in the electrolyte helps in enhancing the reduction of $\text{ReO}_4^-$ ions through formation of a 1:1 rhenium–oxalato complex. The $^{188}$Re deposit on the electrode was dissolved in 0.1 M HCl to yield perrhenic acid, which was neutralized and passed through an alumina column for further purification. The recovered $^{188}$Re had high radiochemical (> 97%) and radionuclidic purity (> 99.99%) and was suitable for radiolabeling various biomolecules. Repeated electrochemical separation of $^{188}$Re from the same stock solution of $^{188}$W could be demonstrated for a period of 6 months and reproducible results were obtained.

The feasibility of developing clinical scale $^{188}$W/$^{188}$Re column chromatographic generators using nanosorbents such as TiP, nano-ZrO$_2$ and •-Al$_2$O$_3$ was also explored in our laboratory [1, 21]. A comparative evaluation of the nanosorbents was carried out and •-Al$_2$O$_3$ was identified as the best choice for preparation of $^{188}$W/$^{188}$Re generator since this material exhibited highest sorption capacity for $^{188}$W ions (~ 300 mg W/g) [1, 22]. Leaving aside the difference in sorption capacity, all the generators developed using nanosorbents yielded $^{188}$Re with high radiochemical (> 99%) and radionuclidic purity (> 99.99%) and were suitable for use in clinical context without post-elution concentration and purification procedures.
Conclusions
In summary, emerging concepts in radionuclide generator technology has been described, which are expected to make captivating advances in the field of nuclear medicine. The electrochemical separation approach was demonstrated as an innovative strategy for the development of clinically useful $^{90}$Sr/$^{90}$Y, $^{188}$W/$^{188}$Re and $^{99}$Mo/$^{99m}$Tc radionuclide generators. Compared with conventional methods, the electrochemical method provides higher yields as well as higher radioactive concentration of the daughter product, good reproducibility and acceptable product purity. Also, the recent advances in material science have paved the way for synthesis of a wide variety of nanosorbents through different routes. These nanosorbents have been used for preparation of clinically useful $^{68}$Ge/$^{68}$Ga, $^{188}$W/$^{188}$Re and $^{99}$Mo/$^{99m}$Tc radionuclide generators. The utility of $^{68}$Ge/$^{68}$Ga generator prepared using nanosorbents has actually been demonstrated for cancer imaging at Tata Memorial Hospital, Mumbai.

While the advances made so far are exciting and efforts to develop new generation of radionuclide generators are evolving persistently, we still have a long way to go in terms of regular utilization of these novel generator systems in clinical context. Completing the technology development as well as establishing the economics of the approach is the cornerstone for the survival and strength of such new approaches. Nevertheless, with sustained efforts of all stakeholders, including, radiopharmacists, radiochemists, system designers, automation engineers, nuclear medicine physicians and regulators, the technological and regulatory barriers can be surmounted and the potential rewards at the end are expected to be substantial.

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