

## Original Article

# Design, construction and testing of a low-cost automated $^{68}\text{Ga}$ -labeling synthesis unit for clinical use

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**Abstract:** The interest in  $^{68}\text{Ga}$  labeled PET probes continues to increase around the world. Widespread use in Europe and Asia has led to great interest for use at numerous sites in the US. One barrier to entry is the cost of the automated synthesis units for relatively simple labeling procedures. We describe the construction and testing of a relatively low-cost automated  $^{68}\text{Ga}$ -labeling unit for human-use. We provide a guide for construction, including part lists and synthesis timelists to facilitate local implementation. Such inexpensive systems could help increase use around the globe and in the US in particular by removing one of the barriers to greater widespread availability. The developed automated synthesis unit reproducibly synthesized  $^{68}\text{Ga}$ -DOTATOC with average yield of  $71 \pm 8\%$  and a radiochemical purity  $\geq 95\%$  in a synthesis time of  $25 \pm 1$  minutes. Automated product yields are comparable to that of manual synthesis. We demonstrate in-house construction and use of a low-cost automated synthesis unit for labeling of DOTATOC and similar peptides with  $^{68}\text{Ga}$ .

**Keywords:**  $^{68}\text{Ga}$  Gallium, peptide labeling, automated synthesis, DOTATOC

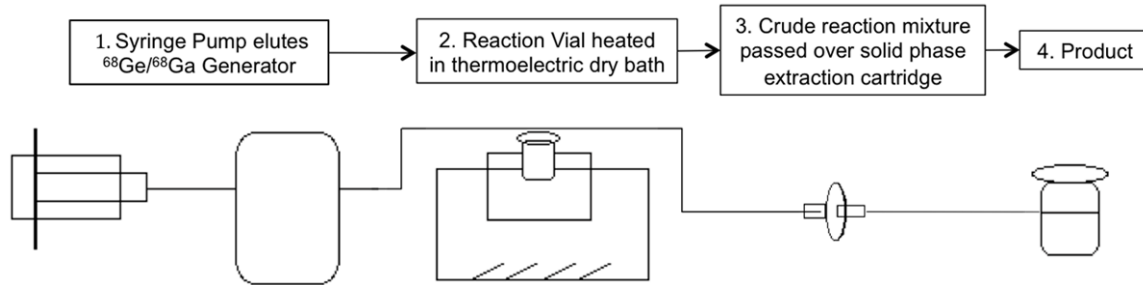
## Introduction

The interest in  $^{68}\text{Ga}$  ( $^{68}\text{Ga}$ )-labeled peptides and biologicals for PET imaging continues to grow around the world, due to the favorable characteristics of  $^{68}\text{Ga}$  [1]. Unlike many other PET imaging isotopes,  $^{68}\text{Ga}$  can be obtained on-demand from a small portable generator without the need for a local cyclotron [2]. In addition, the radiometal easily labels to cyclic conjugates, and its 68-minute half-life makes it ideal for PET imaging with probes of short biological half-life [3]. Recent use of  $^{68}\text{Ga}$ -DOTATOC and  $^{68}\text{Ga}$ -DOTATATE at various sites in the United States as an Investigational New Drug, along with orphan drug status granted to  $^{68}\text{Ga}$ -DOTATOC by the US FDA in 2013 continues to move Gallium-labeled peptides from research use to clinical use in the US.

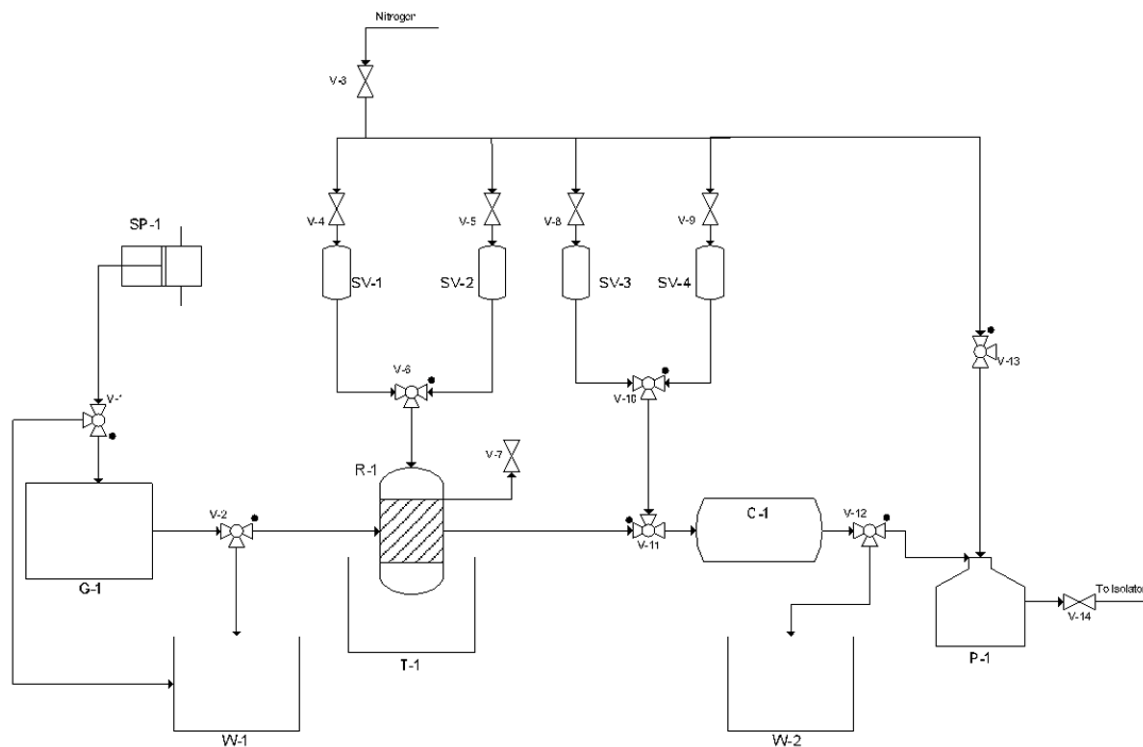
While manual methods of labeling may be appropriate for a research setting, transitioning to the clinic setting mandates reproducible

automated manufacturing and provisions to minimize operator radiation exposure, especially as the number of patients scanned at each site increases [4]. Some clinical facilities now employ automated synthesis units for  $^{68}\text{Ga}$ -labeling of peptides, such as DOTATOC, to prevent undue radiation to the radiopharmacy staff. However, commercial automated synthesis units typically cost in excess of fifty thousand dollars. This high start-up cost can be prohibitive and may leave institutions with no other option but to stick with manual synthesis, and the associated higher operator radiation exposure. We present a design of a low-cost automated synthesis unit for labeling peptides with  $^{68}\text{Ga}$ , which can be assembled for a fraction the cost of commercially available units. Additionally, we provide detailed information of parts, assembly methods, and time-lists to facilitate local implementation of the design. To our knowledge, this is the first time the design and construction of a  $^{68}\text{Ga}$ -labeling unit is

## Constructing a low-cost automated $^{68}\text{Ga}$ -labeling synthesis unit



**Figure 1.** Synthesis Procedure of  $^{68}\text{Ga}$ -labeled peptides. 1. Hydrochloric acid is passed through the generator. 2. The middle fraction of the generator eluant is introduced to the reaction vial, where buffer and peptide are already present in the reaction vial. 3. Separation cartridge allows separation of  $^{68}\text{Ga}$ -collid and  $^{68}\text{Ge}$  from  $^{68}\text{Ga}$ -labeled peptide. 4.  $^{68}\text{Ga}$ -labeled peptide is eluted off the cartridge using Ethanol. Saline is added to reaction in order to achieve physiological conditions.



**Figure 2.** Process flow diagram of automated synthesis unit. Fluid pathways are indicated by lines connecting SP (syringe pump), G (generator), T (thermoelectric heat bath), C (cartridge), V (valve), SV (solvent vial), W (waste), and P (product vial). Normally closed position for three-way valves is indicated by dot.

describe which does not rely on modification of a commercial synthesis box.

The design of the automated synthesis unit models the fundamental labeling methods of a manual synthesis and standard techniques of current macro-scaled units used to make radiopharmaceuticals, as shown in the schematic in **Figure 1**. The primary design consideration, as with all reactions using large amounts of radio-

activity, was to automate the synthesis such that the unit, and thus radiation could be shielded in a lead hot-cell, to minimize the operator's radiation exposure. The design presented gives the operator full remote control from outside the hot-cell where the system can be monitored and manipulated from a linked computer. Finally, the design can be readily modified for use with other radiometals, such as  $^{64}\text{Cu}$  or  $^{89}\text{Zr}$ .

# Constructing a low-cost automated $^{68}\text{Ga}$ labeling synthesis unit

## Materials and methods

### *Design and construction of the automated synthesis unit*

The components of the synthesis unit was chosen based on the dimensional constraints of its lead-shielded hot cell, (16.5" × 28" × 10.75"), functionality and price (Please refer to the [Supplemental Material](#) for detailed parts list). To mount and organize the components of the synthesis unit, a pegboard (McMaster Carr, Princeton, NJ) was chosen as the main structural support. The unit was assembled by first mounting the solenoid valves; their electrical hardware, including a 32-Channel 24 Volt, Sourcing Digital Output Module (National Instrument, Woburn, MA); a CompactDAQ 1-slot USB Chassis (National Instrument, Woburn, MA); and a 37-pin D-sub terminal block (National Instrument, Woburn, MA). Next, a thermoelectric dry bath and syringe pump were mounted and fixed within the pegboard framework and connected to the computer. Lastly the tubing was connected according to the process flow diagram show in **Figure 2**. Waste containers were designed with long tubing lines such that they could sit inside an adjacent waste hot-cell to reduce the operator exposure for a quick reset of the unit for consecutive use.

Fluid delivery was primarily achieved by using nitrogen process gas (Airgas, Cambridge, MA) to transfer solvents through Teflon tubing (Supleco, Bellefonte, PA). Tubing served to connect the major components and enclose the process. Solenoid valves (Burkert Fluid Control Systems, Ingelfingen, Germany) were utilized in order to contain and transfer the solvents from the reaction vials and through the system. Due to undesirability of having process gas in the generator lines, a programmable syringe pump (New Era Syringe Pump Systems Inc.) was used to push HCl through the generator.

A thermoelectric dry bath (Torrey Pines, Torrey Pines, CA) was used to heat the reaction solution to 100°C and drive the  $^{68}\text{Ga}$  incorporation into chelate. This thermoelectric dry bath was chosen to house the lyophilized kit or reaction vial for its ability to rapidly heat, shake and cool the reaction solution. A custom-made aluminum heat block was created to securely hold a 5 mL or 10 mL reactor vial and allow for optimal heat transfer.

Purification of the reaction mixture was performed by slowly passing the cooled reaction fluid through a single use separation C-18 solid-phase extraction cartridge (Sep-Pak Light Waters, Milford, MA) followed by elution with ethanol.

A custom made software with graphical interface was developed in house using LabVIEW (National Instrument, Woburn, MA) to control the mechanical components and different modules of the unit. Time lists were developed for the labeling procedure, daily generator elution, and post synthesis box cleaning (See [Supplemental Material](#) for full time lists; the proprietary software may be obtained upon request from the corresponding author).

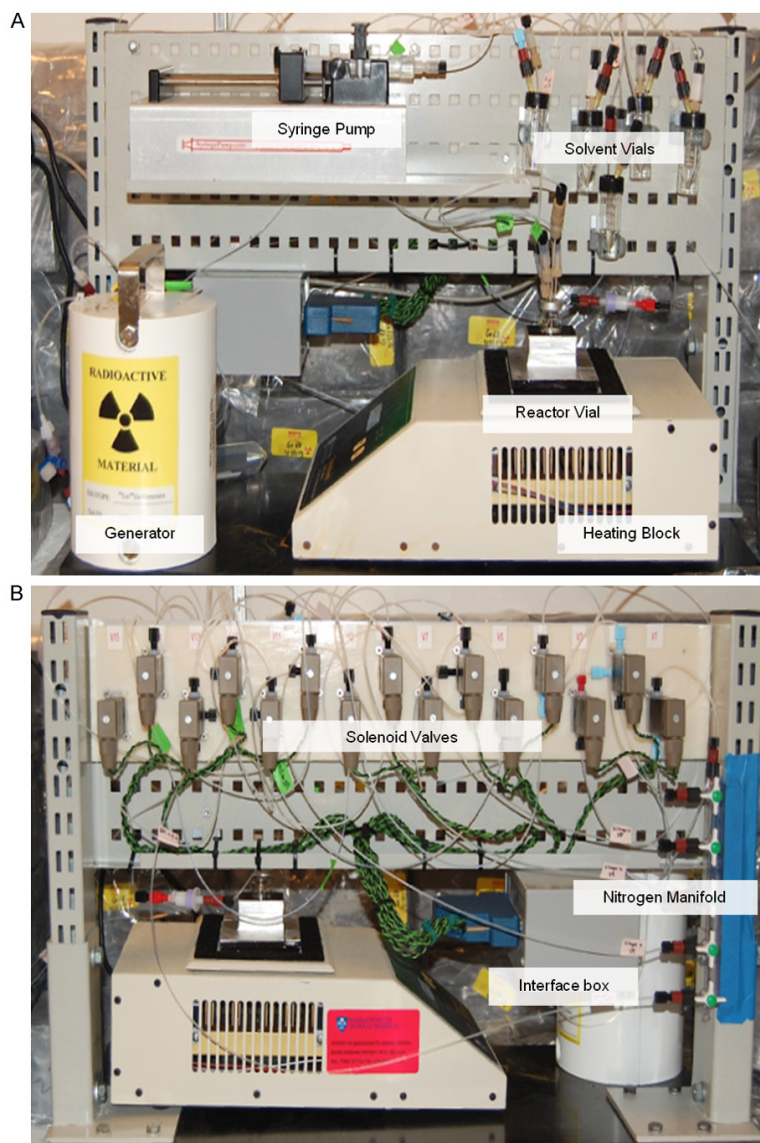
### *Solvents and reagents*

TraceSELECT® Grade (<1 ppb metal impurity) 99% hydrochloric acid (Fluka, Sigma Aldrich, Pittsburgh, PA) was diluted to a concentration of 0.6 M. All water used in dilutions and chemical prep was >18.2 MΩ·cm water (25°C, Milli-Q, Millipore, Billerica, MA). Trace metals were further removed from the water by passing through Chelex® resin (Bio-Rad Laboratories, Hercules, CA.) Lyophilized kits containing 80 µg DOTATOC (edotreotide) and a sodium acetate buffer were obtained from InviCRO (Cambridge, MA). 200 proof Ethanol (American Bioanalytical, Natick, MA) was used to elute the C18 solid-phase extraction cartridge.

### *Labeling procedure*

The reaction is carried out by first eluting the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator (iTHEMBA, South Africa) using 0.6 M hydrochloric acid (HCl). A three step fractionation method [5], is used where only the second fraction containing 2 mL of the eluant, is passed to the reaction vial. The synthesis unit can accommodate other commercially available  $^{68}\text{Ge}/^{68}\text{Ga}$  generators. However, the HCl concentration and sodium acetate concentration in the reaction solution should be adjusted accordingly. The reaction entails heating the contents of the lyophilized DOTATOC and sodium acetate with the eluent for 15 minutes at 100°C, with continuous shaking. The reaction vial is then rapidly cooled to 30°C and the reaction mixture is pushed through a solid-phase extraction cartridge (Sep-Pak, Waters, Milford, MA). Distilled water is introduced to

## Constructing a low-cost automated $^{68}\text{Ga}$ -labeling synthesis unit



**Figure 3.** Front and back (A, B) view of synthesis unit. The unit was designed such that the back of the unit would not need to be accessed on routine basis. All single use components needed for cleaning and reaction can be easily accessed and replaced from the front.

rinse the reactor and connecting tubing of any residual product. Lastly, 200 proof Ethanol is slowly passed through the cartridge to elute the final product. Normal saline (Hospira, Lake Forest, IL) is added to the eluant to reach a 10% ethanol concentration in the final synthesis stock solution (schematic in **Figure 1**).

### Unit validation

To test and optimize the unit time-lists, insulation, and fluid transfer, cold runs with distilled water, bypassing the generator, were performed. Subsequently, 6 validation hot runs

using the  $^{68}\text{Ga}$  eluate from the generator were used to test the labeling efficacy and product specifications.

### *Chemical purity of $^{68}\text{Ga}$ -DOTATOC with high pressure liquid chromatography (HPLC)*

The HPLC system consists of Agilent1100 quaternary pump with degasser (Germany) equipped with Variable UV detector and gamma flow monitor. The samples were run on Phenomenex Gemini (3  $\mu\text{m}$ ; 4.6  $\times$  150 mm) reverse phase C18 column with flow rate of 1.2 mL/min. The mobile phase consisted of a mixture of 68 volume of: 0.1% trifluoroacetic acid (TFA) and 1% acetonitrile (ACN) in water and 32 volumes of 0.1% TFA in (ACN). Samples were analyzed using a 10  $\mu\text{L}$  injection. A 0.5 mg/mL dilution of  $^{69}\text{Ga}$ -DOTATOC acetate in water is used as the reference standard.

### *Testing radiochemical purity and $^{68}\text{Ga}$ -incorporation before radiotracer release using (Normal-phase TLC)*

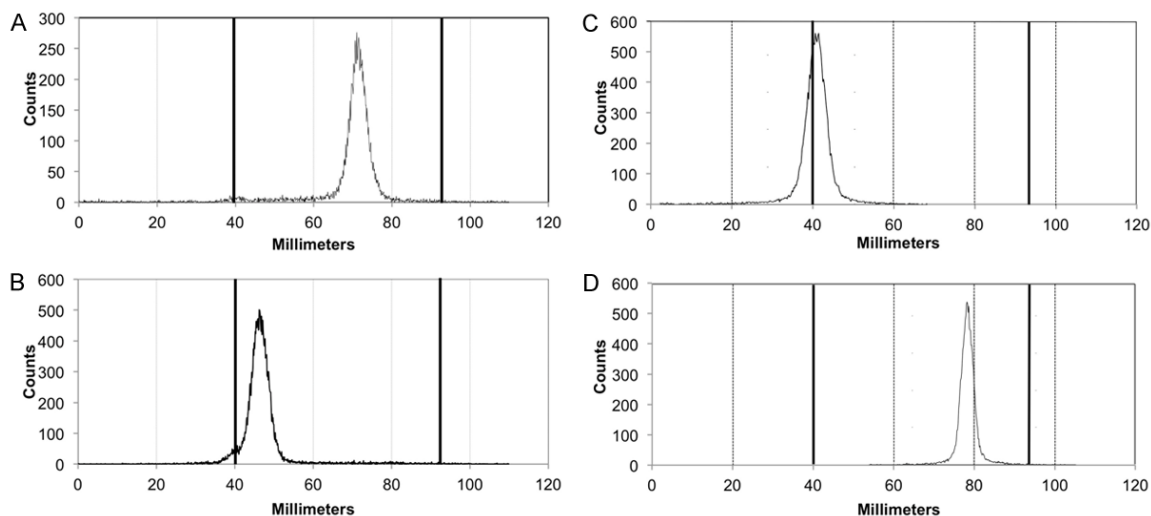
The final product was assessed for radiochemical purity (RCP) via thin layer chromatography (TLC). TLC was conducted using alumina-backed silica gel, and two mobile phases, 0.1 M sodium citrate

(Sigma Aldrich, St. Louis, MO) and 1 M ammonium acetate/methanol (1:1 v/v) (Sigma Aldrich, St. Louis, MO) [6, 7]. The RCP was determined as the area of the peak with  $R_f$  of  $^{68}\text{Ga}$ -DOTATOC divided by the area sum of all the peaks. Plates were analyzed using a radio-TLC plate reader (AR-2000, Bioscan).

### $^{68}\text{Ge}$ breakthrough

To assess  $^{68}\text{Ge}$  breakthrough the daughter radionuclide,  $^{68}\text{Ga}$ , was sought for using gamma spectrum analysis of elute, i.e. after complete decay of  $^{68}\text{Ga}$  eluted from the generator, 1

## Constructing a low-cost automated $^{68}\text{Ga}$ Gallium-labeling synthesis unit



**Figure 4.** Representative TLC chromatogram. Origin at 40 mm, (Rf = 0) solvent front at 90 mm (Rf = 1). Radiochemical purity >95%. A. Mobile phase, ammonium acetate, with true peak of  $^{68}\text{Ga}$ -DOTATOC at Rf = 0.7 and impurity at Rf = 0.1. B. Mobile phase, sodium citrate, with true peak of  $^{68}\text{Ga}$ -DOTATOC at Rf = 0.1 and impurity at Rf = 0.7. C. Mobile phase, ammonium acetate, with true peak of free  $^{68}\text{Ga}$  at Rf = 0.05. D. Mobile phase, sodium citrate, with true peak of free  $^{68}\text{Ga}$  Rf = 0.8.

week after elution. The samples of 1 ml were loaded in 5 ml scintillation vials and were counted for 6 hours. The 511 KeV photon emissions were measured using a gamma-counter (Wizard 2480, PerkinElmer Downers Grove, IL USA), on a weekly basis.

### *Xenograft model and PET imaging*

All animal experiments were performed in accordance with Institutional Animal Care and Use Committee (IACUC) guidelines. AR42J xenografts were prepared as previously reported [8]. Briefly, AR42J (ATCC, Manassas, VA), an SSTR-expressing rat pancreatic carcinoma, were mixed with Matrigel (BD Bioscience, San Jose, CA) and were subcutaneously injected into male Nu/Nu mice. Once tumors reached a diameter of 5-10 mm, mice were imaged using the synthesized  $^{68}\text{Ga}$ -DOTATOC. PET imaging was conducted using an Argus microPET/CT (Sedecal, Madrid, Spain) for 55 minutes in list mode after injection of approximately 200  $\mu\text{Ci}$   $^{68}\text{Ga}$ -DOTATOC via the tail-vein as previously reported [8, 9]. The PET images were reconstructed using 2D-OSEM algorithm and analyzed as previously described [8, 9].

### *$^{68}\text{Ga}$ -DOTATOC temporal biodistribution in xenografts*

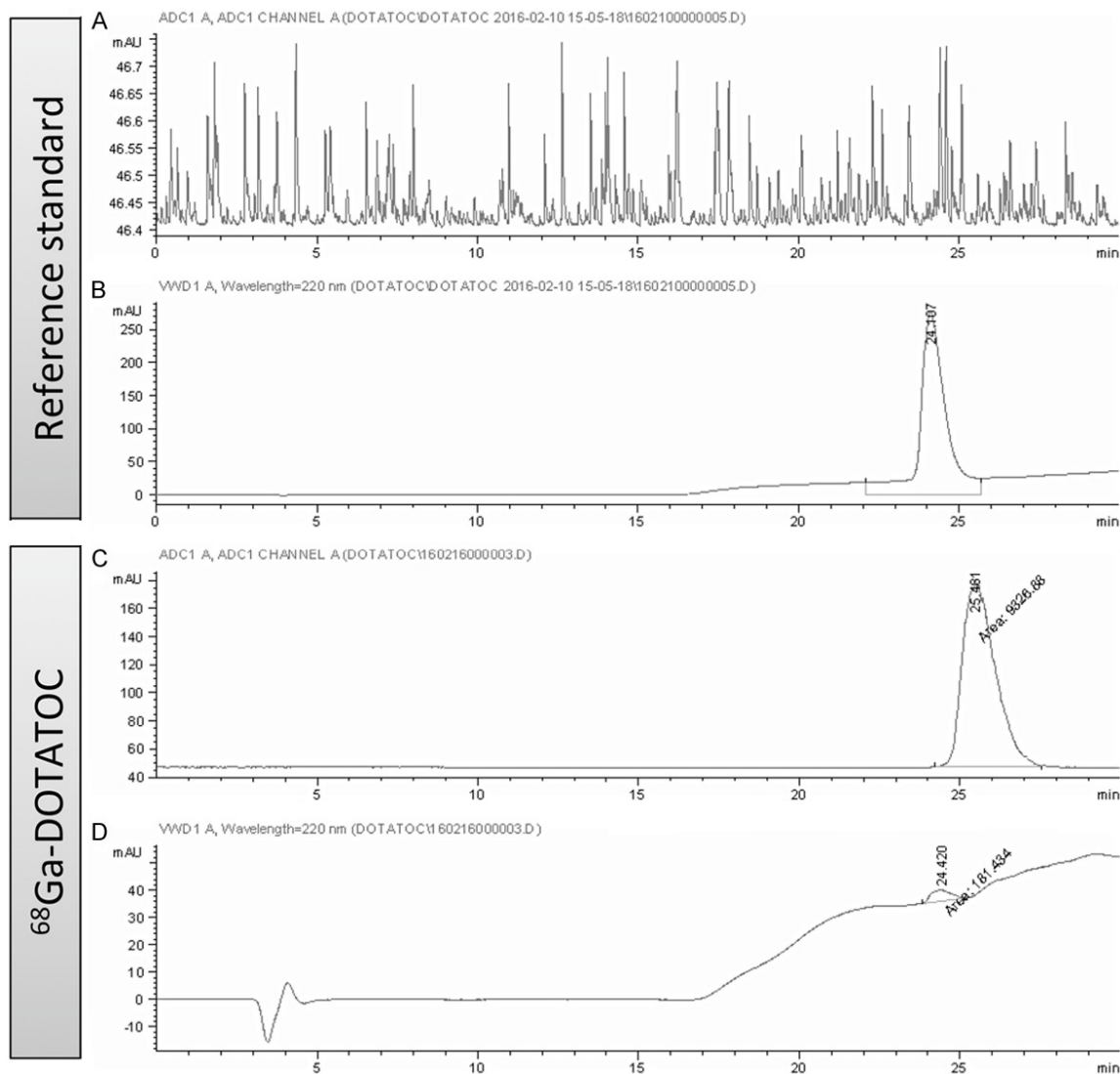
Nude mice bearing AR42J xenografts were injected with ~50  $\mu\text{Ci}$  of  $^{68}\text{Ga}$ -DOTATOC in 0.2

ml volume and sacrificed at 15, 60, and 120 minutes. Organs were extracted and tissue samples were measured on a Wizard 2480 gamma counter (Perkin-Elmer). The percent injected dose per gram tissue (%ID/g) was determined for all the organs.

### *PET/MRI imaging of human subjects*

The Institutional Review Board (IRB) of our hospital has approved human trials. Here we present representative images and quantitative data from a healthy volunteer enrolled in a clinical trial at our institution. We use  $^{68}\text{Ga}$ -DOTATOC for clinical trials using and extended access investigation new drug (IND) application with FDA. PET-MRI studies were acquired with a 3 Tesla Biograph mMR scanner (Siemens Medical Solutions, Knoxville, TN) with a 16-channel head and neck surface coil and three to five 12-channel body coils. The PET-MRI acquisitions were performed at 15, 60, 120 and 240 minutes from approximately 10 mCi  $^{68}\text{Ga}$ -DOTATOC injection. PET acquisition was performed with a 26 cm z-axis field of view and 30% overlap between adjacent table stations. Four to six bed positions were acquired based on patient height. MRI acquisitions were simultaneously with PET acquisition starting from the level of the mid-thigh and moving toward the head. PET data underwent automatic attenuation correction with attenuation maps generated from the

## Constructing a low-cost automated $^{68}\text{Ga}$ -labeling synthesis unit



**Figure 5.** Representative HPLC chromatograms on reference standard and  $^{68}\text{Ga}$ -DOTATOC. (A) Radiometric graph on the reference standard ( $^{69}\text{Ga}$ -DOTATOC) which contains a stable gallium isotope just demonstrates random background noise. (B) A sharp UV peak is seen at approximately 24 minutes after injection sample. (C) Radiometric chromatogram shows a radioactive peak at around 25 minutes which corresponds to a small UV peak at 24.5 minutes seen on (D).

two-point Dixon sequence. The sample images were analyzed using a TrueD Siemens workstation and SUVmean for different organs was calculated using a 70% iso-contour.

### Results

#### *Automated synthesis unit*

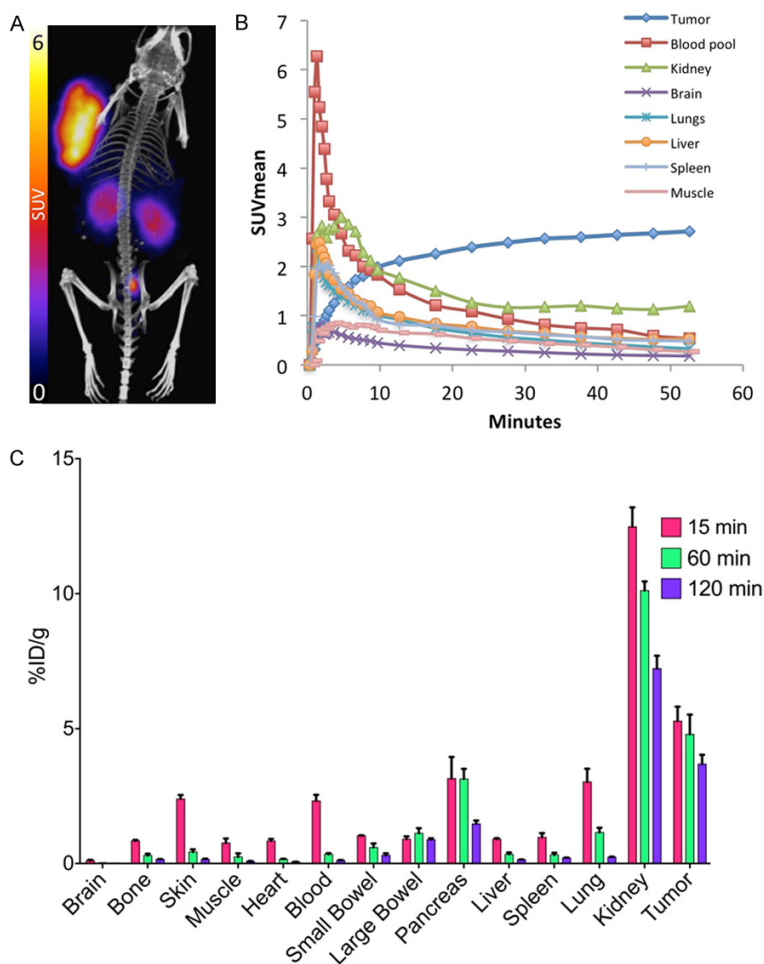
The assembled unit with labeled components is detailed in **Figure 3**. All parts and components were purchased for less than \$10,000 total, excluding the  $^{68}\text{Ge}/^{68}\text{Ga}$  Generator and software development cost. The developed

software is available for free upon request from the corresponding author and therefore the software development cost is not included in the total unit cost. The detailed parts list can be found in the [Supplemental Material](#).

#### *Synthesis unit validation*

A total of 6 development and 7 recent clinical radiosynthesis runs were analyzed. The decay corrected product yield was  $14.4 \pm 1.7$  mCi ( $71 \pm 8\%$ ) with mean pH of  $6.8 \pm 0.2$  and  $15.5 \pm 1.7$  mCi ( $77 \pm 8\%$ ) with mean pH of  $6.6 \pm 0.1$  for the development and clinical runs, respectively.

## Constructing a low-cost automated $^{68}\text{Ga}$ -labeling synthesis unit



**Figure 6.** A. Representative 3D MIP reconstruction of  $^{68}\text{Ga}$ -DOTATOC PET/CT of nu/nu mouse with AR42J xenograft, demonstrates high uptake in the tumor relative to other organs. B. Representative time activity curves in a mouse with AR42J tumor showing continuous increase in tumor activity while blood pool and other organs decrease over time. The equilibrium is reached at around 30 minutes from injection of  $^{68}\text{Ga}$ -DOTATOC. C. Organ biodistribution bar graph shows significant decrease in the blood pool and normal organ activities but relatively constant tumor uptake. The tumor to blood pool ratio increases over time.

The final formulation was  $^{68}\text{Ga}$ -DOTATOC in a 10 mL solution of 10% ethanol in normal saline. Properties of the acceptable product included a physiological pH of 6.5-7, a clear colorless solution free of particles, <0.01% acetone by volume, and endotoxins <3.0 EU/ml. The total automated synthesis time was  $28 \pm 1$  minutes compared to  $35 \pm 2$  minutes of manual synthesis.

### Quality control

To established chemical purity of the product HPLC was used. We used  $^{69}\text{Ga}$ -DOTATOC as the

reference standard and regularly test batches of  $^{68}\text{Ga}$ -DOTATOC for chemical purity. Using the method described we are able to match the retention time of the radiometric peak with the reference standard UV peak (at 220 nm) for a chemical identification test. **Figure 5** shows a sample chromatogram where the UV and radiometric peak of the  $^{68}\text{Ga}$ -DOTATOC matches the UV peak of the reference standard at 24-25 minutes after sample injection.

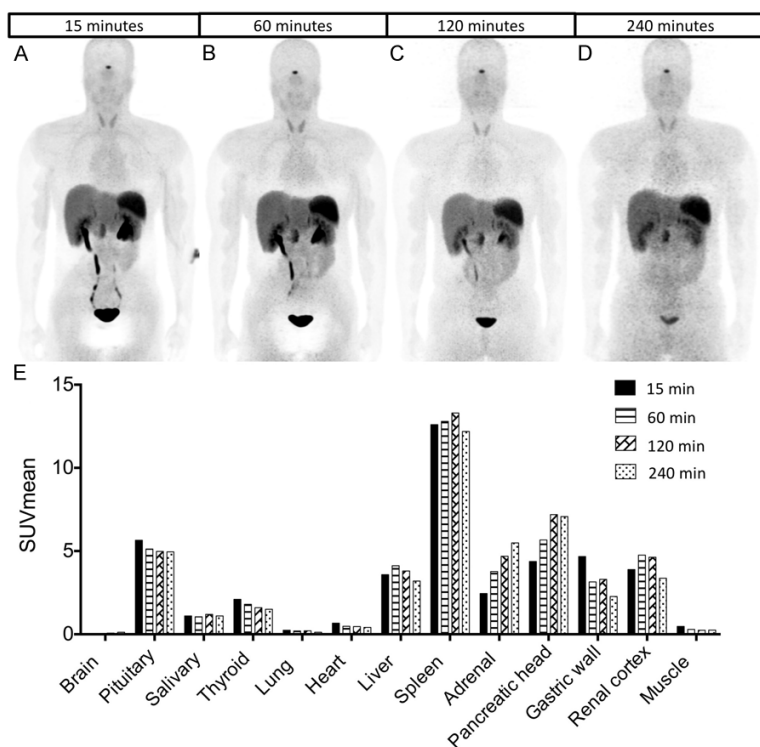
Radiochemical purity was measured for synthesis runs using TLC before release of product for injection. The mean RCP of the final product was  $98.7 \pm 1.2$  ( $R_f = 0.95 \pm 0.04$ ) and  $96.2 \pm 1.8\%$  ( $R_f = 0.91 \pm 0.03$ ) for the development and sample clinical synthesis runs. **Figure 4** demonstrates representative TLC chromatograms of both  $^{68}\text{Ga}$ -DOTATOC and free unbound  $^{68}\text{Ga}$  using both mobile phases.

Based on results documented from regular generator elution in the first 6 months of use the average  $^{68}\text{Ge}$  activity in the samples was  $6.6 \times 10^{-4} \pm 1.5 \times 10^{-5}$   $\mu\text{Ci/ml}$  or approximately  $6.88 \times 10^{-5}\%$  of the elution activity which is significantly lower than allowable limits of  $2 \times 10^{-3}\%$  stated in our IND for  $^{68}\text{Ga}$ -DOTATOC.

### $^{68}\text{Ga}$ -DOTATOC microPET/CT imaging

Static  $^{68}\text{Ga}$ -DOTATOC PET/CT results confirmed the affinity of the labeled peptide to AR42J xenografts, which express high levels of somatostatin receptor type 2, as we have shown previously [8]. A representative 3D reconstructed maximum intensity projection image and time activity curves are shown in **Figure 6**. As expected except the scan the blood pool and every normal organ initially show a rapid upstroke of

## Constructing a low-cost automated $^{68}\text{Ga}$ Gallium-labeling synthesis unit



**Figure 7.**  $^{68}\text{Ga}$ -DOTATOC PET in a healthy human subject at 15 to 240 minutes after injection of radiotracer. A-D. Representative maximum intensity projection images demonstrate overall similar biodistribution of the  $^{68}\text{Ga}$ -DOTATOC from 15-240 minutes after tracer injection. E. Quantitative analysis of the organs demonstrates approximately similar level of tracer uptake in the organs from 15-240 minutes after tracer injection. However, there is slight increase in the uptake of adrenals and pancreatic head which is likely due to low level SSTR expression in these organs.

activity after injection which is due to high blood pool activity. Once the activity is distributed to other compartments and elimination begins there is consistent decrease in the  $^{68}\text{Ga}$ -DOTATOC uptake in almost every organ. The tumor uptake on the other hand consistently increases until the equilibrium is reached at around 30 minutes from injection.

### $^{68}\text{Ga}$ -DOTATOC biodistribution

We assessed the biodistribution of  $^{68}\text{Ga}$ -DOTATOC in nude mice bearing AR42J xenografts at 15, 60 and 120 minutes. Compared to the 15 minute time point when the blood pool activity is still high and equilibrium is not reached the activity of almost every organ significantly decreases at 60 and 120 minutes. The tumor activity does not significantly change between early and late time points, but the tumor to blood pool ratio significantly increases. The uptake in the kidneys are higher in the biodistribution study compared to the TAC from

the dynamic PET imaging which is most likely due to included renal collecting systems in the biodistribution studies which contain high concentration of eliminated  $^{68}\text{Ga}$ -DOTATOC in the excreted urine (Figure 6).

### $^{68}\text{Ga}$ -DOTATOC PET in human subjects

We have presented a  $^{68}\text{Ga}$ -DOTATOC PET of a normal healthy subject at multiple time points up to 4 hours from injection. As expected from  $^{68}\text{Ga}$ -DOTATOC the uptake values in the normal organs remain relatively similar from 15-240 minutes. The uptake in the pancreatic head and adrenal slightly increases over time, which is likely due to small number SSTR receptors expressed in both of these organs (Figure 7).

### Discussion

We demonstrated construction of a custom-made automated synthesis unit, assembled for a fraction of the cost of commercial modules typically employed for similar synthesis. The presented design uses the same key principal steps in a manual synthesis including  $^{68}\text{Ge}/^{68}\text{Ga}$  generator elution/fractionation, reaction heating and product purification. Previous literature has focused on automated  $^{68}\text{Ga}$  labeling of the peptides using commercial  $^{68}\text{Ga}$  synthesis modules or modification of an existing commercial synthesis module for  $^{68}\text{Ga}$  labeling [4, 10, 11]. However, the cost of commercial synthesis modules is often prohibitive for low volume  $^{68}\text{Ga}$ -peptide use sites, and leaves this area of clinical research and translation financially inaccessible to many facilities. The synthesis unit we presented precludes the need for in-house commercial synthesis units, which can cost between 5-10 times more. We hope reducing the startup costs enable an increasing number of institutions in the United States and around the globe to reproducibly label peptides and biologicals with  $^{68}\text{Ga}$  for



human research and clinical PET imaging, while minimizing the operator radiation dose. The presented automated unit eases the certification and documentation burden for each synthesis, given the documented time-stamped steps recorded by the software. The unit components can either be sterilized and reused, or are single use disposables such as the chemical/reaction vials, C-18 separation cartridge, and HCl syringe. After approximately 50 synthesis runs, the Teflon tubing should be replaced for unit maintenance.

An additional major advantage of an automated system over manual synthesis is the increased reproducibility by reducing operator variability [4, 10, 11]. This is particularly important in clinical use, both with respect to GMP compliance and for maintaining the high specific activity requirement for accurate PET quantitation. Our validation runs demonstrated highly reproducible synthesis yields with radiochemical purity of >95%. To date, we have synthesized over 100 doses of <sup>68</sup>Ga-DOTATOC for preclinical use, and for clinical scans using iThemba and ITG generators. We have not observed any synthesis failure related to synthesis unit. The yield and radiochemical purity of all the synthesis runs were within the limits mentioned in the results. All synthesis runs passed the standard quality control test, typically implemented in a radiopharmacy including TLC for radiochemical purity, sterility, endotoxin, and residual solvents tests. As we demonstrated, automated synthesis was approximately 7 minutes faster than manual synthesis on average.

In conclusion, we showed that a custom made fully automated synthesis unit that can be used to prepare <sup>68</sup>Ga labeled peptides for clinical use. This unit has the benefit of remote and reproducible synthesis, in addition to costing less than \$10,000.

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