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(54) Title: METHOD FOR EXTRACTION AND PURIFICATION OF 68GA

(57) Abstract: Disclosed herein are methods preparing a purified, carrier-free 68Ga solution. Tire present disclosure also provides systems for preparing a purified, carrier-free 68Ga solution. The present disclosure also provides compositions comprising the purified, carrier-free 68Ga solutions disclosed herein. Also provided are methods of administering compositions of the present disclosure to a patient in need thereof, for example, for imaging a disease or disorder, such as cancer.



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DESCRIPTION

METHOD FOR EXTRACTION AND PURIFICATION OF ^{68}Ga

The present application claims the priority benefit of United States provisional application number 62/714,190, filed August 3, 2018, the entire contents of which are incorporated herein by reference.

BACKGROUND

I. Field of the Invention

The present invention relates generally to the fields of chemistry and biological imaging. More particularly, it concerns methods for preparing purified ^{68}Ga , systems for preparing purified ^{68}Ga , compositions comprising purified ^{68}Ga , and methods of use thereof.

II. Description of Related Art

The noticeable increase in PET imaging with ^{68}Ga -labeled tracers over recent years has been marginally supported by the increased accessibility of $^{68}\text{Ge}/^{68}\text{Ga}$ generators (Prata, 2012). Gallium-68 conveniently possesses two desirable properties, a short half-life ($t_{1/2}$: 68 min) and a high branching ratio for positron emission (β^+ +: 89%). To date, ^{68}Ga has been widely applied into various pre-clinical and clinical imaging studies. For instance, ^{68}Ga -labeled somatostatin analogs have already demonstrated their value in imaging patients diagnosed with neuroendocrine tumors (Ambrosini and Fanti, 2014; Shamim et al., 2015; Virgolini et al., 2016). Recent reports indicate ^{68}Ga -PSMA is superior to $^{11}\text{C}/^{18}\text{F}$ -Choline in detecting more prostate cancer lesions, especially at lower prostate-specific antigen (PSA) levels in biochemically recurrent patients (Lindenberg et al., 2016; Schwenck et al., 2017). Given these results, the clinical promise of ^{68}Ga -labeled radiopharmaceuticals clearly warrants the need to increase the availability of ^{68}Ga for PET imaging applications.

Although current $^{68}\text{Ge}/^{68}\text{Ga}$ generators can nominally deliver up to 1.85 GBq (50 mCi) of ^{68}Ga per elution, nonetheless ^{68}Ga activity decreases over time due to the decay of the parent nuclide ^{68}Ge ($t_{1/2}$: 271 d). Furthermore, elution efficiencies around 80% of present activity are typical. In addition, the potential breakthrough of ^{68}Ge with eluted ^{68}Ga remains a concern (Belosi et al., 2013). Therefore, cyclotron production of ^{68}Ga not only can provide an alternative way to meet the increasing demand for ^{68}Ga , but also eliminates the possibility of ^{68}Ge breakthrough.

Jensen and Clark reported the first attempt to produce ^{68}Ga using a cyclotron with a liquid target filled with a $^{68}\text{ZnCl}_2$ solution (Jensen and Clark, 2011). Since then, Engle et al. have used a solid natZn target to produce $^{66/68}\text{Ga}$ (Engle et al., 2012). The thermal diffusion method (Tolmachev and Lundqvist, 1996) to recover $^{66/68}\text{Ga}$ from natural Zn foils presents advantages in

processing time when thin (< 0.1 mm) foils are considered (Siikanen, 2013). Pandey et al. tried to optimize ^{68}Ga production through liquid targetry (Pandey et al., 2014). However, due to lengthy ^{68}Ga separation steps reported by Engle et al. along with the relatively low production yields of ^{68}Ga observed using liquid targetry, available ^{68}Ga at end of processing is not significantly higher than generator produced isotope. Recently, medical cyclotron production of ^{68}Ga from a ^{68}Zn solid target has been shown to produce Curie quantities of ^{68}Ga with low levels of ^{68}Ge breakthrough.

Despite the improvement in methods to produce ^{68}Ga , present methods for the purification of ^{68}Ga produced by liquid or solid targetry require lengthy processing times due to the need for multiple purification steps. Due to the short half-life of ^{68}Ga , there is a need for single-step purification protocols that can expediently deliver higher quantities of purified ^{68}Ga for medical imaging applications.

SUMMARY OF THE INVENTION

The present disclosure provides methods for the purification of radionuclide solutions, including ^{68}Ga solutions, and imaging agents prepared by these methods.

In some embodiments, the present disclosure provides methods of preparing a purified, carrier-free ^{68}Ga solution comprising:

- a) obtaining a ^{68}Ga solution to be purified comprising ^{68}Ga ;
- b) contacting the ^{68}Ga solution with an anion-exchange resin; and
- c) eluting the ^{68}Ga from the anion-exchange resin to obtain the purified, carrier-free ^{68}Ga solution.

In some aspects, the method comprises contacting the ^{68}Ga solution to be purified with a single anion-exchange resin. In some aspects, the method does not comprise contacting the ^{68}Ga solution to be purified or the purified, carrier-free ^{68}Ga solution with another ion-exchange resin. In some aspects, the ^{68}Ga in the ^{68}Ga solution to be purified is prepared by synthesizing the ^{68}Ga in the ^{68}Ga solution. In further aspects, a cyclotron is used to synthesize the ^{68}Ga . In further aspects, the cyclotron comprises a metal sample in the form of a liquid target. In still further aspects, the metal sample comprises $^{68}\text{Zn}^{2+}$. In other aspects, the cyclotron comprises a metal sample in the form of a solid target. In further aspects, the metal sample comprises ^{68}Zn . In some aspects, the ^{68}Ga solution to be purified comprises an acid. In further aspects, the acid has a concentration of greater than about 2 N. In still further aspects, the acid has a concentration of from about 3 N to about 10 N, such as about 6 N. In some aspects, the acid is HCl or is derived from the dissociation of HCl. In some aspects, the ^{68}Ga solution to be purified is an aqueous solution.

In some aspects, the anion-exchange resin comprises a phosphonate or a substituted phosphonate. In some aspects the anion-exchange resin comprises a phosphonate, such as dipentyl pentylphosphonate. In some aspects, the methods further comprise washing the anion-exchange resin with a washing solution. In some aspects, the washing step occurs before the eluting step. In some aspects, the washing solution comprises an acid. In some aspects, the acid has a concentration of greater than about 1 N. In further aspects, the acid has a concentration of from about 2 N to about 8 N, such as about 4 N. In some aspects, the acid is HCl or is derived from the dissociation of HCl. In some aspects, the washing solution is an aqueous solution.

In some aspects, eluting comprises contacting the anion-exchange resin with an eluting solution. In some aspects, the eluting solution comprises an acid. In some aspects, the acid has a concentration of from about 0.005 N to about 2 N. In further aspects, the acid has a concentration

from about 0.01 N to about 1 N, such as about 0.05 N. In some aspects, the acid is HCl or is derived from the dissociation of HCl. In some aspects, the eluting solution is an aqueous solution.

In some aspects, the purified, carrier-free ^{68}Ga solution has an activity of from about 37 MBq to about 370 GBq. In further aspects, the purified, carrier-free ^{68}Ga solution has an activity of from about 370 MBq to about 370 GBq. In still further aspects, the purified, carrier-free ^{68}Ga solution has an activity of from about 3.7 GBq to about 370 GBq. In some aspects, the purified, carrier-free ^{68}Ga solution comprises less than about 1 $\mu\text{g}/\text{GBq}$ of zinc. In further aspects, the purified, carrier-free ^{68}Ga solution comprises less than about 0.1 $\mu\text{g}/\text{GBq}$ of zinc. In still further aspects, the purified, carrier-free ^{68}Ga solution comprises less than about 0.01 $\mu\text{g}/\text{GBq}$ of zinc. In some aspects, the purified, carrier-free ^{68}Ga solution comprises less than about 10 $\mu\text{g}/\text{GBq}$ of iron. In further aspects, the purified, carrier-free ^{68}Ga solution comprises less than about 1 $\mu\text{g}/\text{GBq}$ of iron. In still further aspects, the purified, carrier-free ^{68}Ga solution comprises less than about 0.5 $\mu\text{g}/\text{GBq}$ of iron. In some aspects, the purified, carrier-free ^{68}Ga solution comprises less than about 1 $\mu\text{g}/\text{GBq}$ of germanium. In further aspects, the purified, carrier-free ^{68}Ga solution comprises less than about 0.01 $\mu\text{g}/\text{GBq}$ of germanium. In still further aspects, the purified, carrier-free ^{68}Ga solution comprises less than about 0.0001 $\mu\text{g}/\text{GBq}$ of germanium.

In some aspects, the purified, carrier-free ^{68}Ga solution has a specific activity of greater than about 25 GBq/ μg . In further aspects, the purified, carrier-free ^{68}Ga solution has a specific activity of from about 25 GBq/ μg to about 100,000 GBq/ μg . In further aspects, the purified, carrier-free ^{68}Ga solution has a specific activity of from about 100 GBq/ μg to about 100,000 GBq/ μg . In further aspects, the purified, carrier-free ^{68}Ga solution has a specific activity of from about 1,000 GBq/ μg to about 100,000 GBq/ μg . In further aspects, the purified, carrier-free ^{68}Ga solution has a specific activity of from about 10,000 GBq/ μg to about 80,000 GBq/ μg . In further aspects, the purified, carrier-free ^{68}Ga solution has a specific activity of from about 25,000 GBq/ μg to about 50,000 GBq/ μg . In still further aspects, the purified, carrier-free ^{68}Ga solution has a specific activity of from about 31,000 GBq/ μg to about 36,000 GBq/ μg . In some embodiments, the present disclosure provides purified, carrier-free ^{68}Ga solutions prepared according to methods disclosed herein.

In some embodiments, the present disclosure provides systems for preparing a purified, carrier-free ^{68}Ga solution comprising:

- a) a solid target comprising ^{68}Zn ;
- b) a cyclotron, wherein the solid target is irradiated using the cyclotron; and
- c) an anion-exchange resin.

In some aspects, the system comprises a single anion-exchange resin. In some aspects, the system does not comprise another ion-exchange resin. In some aspects, the anion-exchange resin comprises a phosphonate or a substituted phosphonate. In some aspects, the anion-exchange resin comprises a phosphonate, such as dipentyl pentylphosphonate. In some aspects, the purified, carrier-free ^{68}Ga solution has a specific activity of from about 25 GBq/ μg to about 100,000 GBq/ μg . In further aspects, the purified, carrier-free ^{68}Ga solution has a specific activity of from about 100 GBq/ μg to about 100,000 GBq/ μg . In further aspects, the purified, carrier-free ^{68}Ga solution has a specific activity of from about 1,000 GBq/ μg to about 100,000 GBq/ μg . In further aspects, the purified, carrier-free ^{68}Ga solution has a specific activity of from about 10,000 GBq/ μg to about 85,000 GBq/ μg . In further aspects, the purified, carrier-free ^{68}Ga solution has a specific activity of from about 25,000 GBq/ μg to about 50,000 GBq/ μg . In still further aspects, the purified, carrier-free ^{68}Ga solution has a specific activity of from about 31,000 GBq/ μg to about 36,000 GBq/ μg .

In some embodiments, the present disclosure provides compositions comprising the purified, carrier-free ^{68}Ga solutions disclosed herein. In some aspects, the compositions further comprise a carrier molecule, wherein the carrier molecule is radiolabeled with the ^{68}Ga of the purified, carrier-free ^{68}Ga solution. In further aspects, the carrier molecule is an antibody or a fragment thereof. In other aspects, the carrier molecule is a peptide or a fragment thereof. In other aspects, the carrier molecule is prostate-specific membrane antigen (PSMA), 1,4,7-triazacyclononane- N,N',N'' -triacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), diethylene triamine pentaacetic acid (DTPA), desferrioxamine, DOTA-Tyr(3)-octreotide (DOTATOC), DOTA-Tyr(3)-Tyr(8)-octreotide (DOTATATE), DOTA-1-naphthyl-alanine (DOTANOC), DOTA-benzothienyl-alanine (DOTA-BOC), DOTA-bombesin, DOTA-arginine-glycine-aspartic acid-bombesin (DOTA-RGD-bombesin), NOTA-RGD, 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15)-,11,13-triene-3,6,9-triacetic acid-RGD (PCTA-RGD), DOTA-albumin, DOTA-human epidermal growth factor, 1,4,7-triazacyclononane-1-[methyl(2-carboxyethyl)phosphinic acid]-4,7-bis[methyl(2-hydroxymethyl)phosphinic acid]-integrin $\alpha(\text{IIb})\beta(3)$ -specific cyclic hexapeptide (NOPO-RGDfK), 1,4,7-triazacyclononane-1,4-bis(acetic acid)-7-(2-glutaric acid) (NODAGA), NOPO-NaI(3)-octreotide conjugate (NOPO-NOC), 1,4,7-triazacyclononane-1,4,7-tris[(2-carboxyethyl)methylenephosphinic acid] (TRAP(RGD)₃), or citrate. In further aspects, the carrier molecule is PSMA, DOTATATE, DOTATOC, DOTANOC, or citrate. In some aspects, the carrier molecule is PSMA. In other aspects, the carrier molecule is DOTATATE. In still other aspects, the carrier molecule is citrate. In some

aspects, the carrier molecule targets a human tissue. In some aspects, the human tissue is selected from the following: thyroid, brain, gastrointestinal, pancreas, spleen, kidney, neuroendocrine tumors, renal cell carcinoma, lung cancer, breast cancer, prostate cancer, and malignant lymphoma.

5 In some embodiments, the present disclosure provides methods of imaging comprising administering a composition disclosed herein to a patient. In some aspects, the patient is a mammal. In further aspects, the mammal is a human. In some aspects, the composition is administered more than once. In other aspects, the composition is administered once. In some aspects, the composition is formulated for administration intraarterially, intraarticularly,
10 intracranially, intrapericardially, intraperitoneally, intratumorally, intravenously, intravesicularly, parenterally, via injection, via local delivery, or via localized perfusion. In some aspects, the composition is formulated for administration intravenously. In some aspects, the composition is formulated as a unit dose. In some aspects, the methods further comprise imaging a tumor. In some aspects, the tumor is a neuroendocrine tumor. In some aspects, the tumor expresses elevated
15 levels of PSMA. In further aspects, the tumor is a pancreatic tumor, a prostate tumor, or a lung tumor. In some aspects, the tumor is a pancreatic tumor. In other aspects, the tumor is a prostate tumor. In still other aspects, the tumor is a lung tumor.

In other embodiments, the present disclosure provides methods of preparing a purified, carrier-free ^{68}Ga solution having a specific activity of greater than about 25 GBq/ μg comprising:

- 20 a) obtaining a ^{68}Ga solution to be purified comprising ^{68}Ga ;
b) contacting the ^{68}Ga solution with an ion-exchange resin; and
c) eluting the ^{68}Ga from the ion-exchange resin to obtain the purified, carrier-free ^{68}Ga solution.

25 In some aspects, the method comprises a single ion-exchange resin. In some aspects, the method does not comprise another ion-exchange resin.

In still other embodiments, the present disclosure provides methods of preparing a purified, carrier-free ^{68}Ga solution having a specific activity of greater than about 25 GBq/ μg comprising:

- a) obtaining a ^{68}Ga solution to be purified comprising ^{68}Ga ;
b) contacting the ^{68}Ga solution with an anion-exchange resin; and
30 c) eluting the ^{68}Ga from the anion-exchange resin to obtain the purified, carrier-free ^{68}Ga solution.

In some aspects, the method comprises a single anion-exchange resin. In some aspects, the method does not comprise another ion-exchange resin.

In still other embodiments, the present disclosure provides systems for preparing a purified, carrier-free ^{68}Ga solution having a specific activity of greater than about 25 GBq/ μg comprising:

- 5 a) a solid target comprising ^{68}Zn ;
- b) a cyclotron, wherein the solid target is irradiated using the cyclotron; and
- c) an ion-exchange resin.

In some aspects, the system comprises a single ion-exchange resin. In some aspects, the system does not comprise another ion-exchange resin.

- 10 In still other embodiments, the present disclosure provides systems for preparing a purified, carrier-free ^{68}Ga solution having a specific activity of greater than about 25 GBq/ μg comprising:

- a) a solid target comprising ^{68}Zn ;
- b) a cyclotron, wherein the solid target is irradiated using the cyclotron; and
- c) a single anion-exchange resin.

- 15 In some aspects, the system comprises a single anion-exchange resin. In some aspects, the system does not comprise another ion-exchange resin.

- Other objects, features, and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by
- 20 way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure. The disclosure may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIGS. 1A-1C show HPLC traces of DOTA-Oct labeling tests with cyclotron-produced ^{68}Ga (conditions: pH 4.5, 95 °C for 10 minutes). FIG. 1A shows labeling test with 100 µg of DOTA-Oct and 100 mCi of ^{68}Ga (radiochemical yield = 98.4%, radiochemical purity = 94.2%). FIG. 1B shows labeling test with 50 µg of DOTA-Oct and 100 mCi of ^{68}Ga (radiochemical yield = 99.2%, radiochemical purity = 96.7%). FIG. 1C shows labeling test with 25 µg of DOTA-Oct and 100 mCi of ^{68}Ga (radiochemical yield = 96.5%, radiochemical purity = 88.1%).

FIGS. 2A-2C show HPLC traces of PSMA-11 labeling tests with cyclotron-produced ^{68}Ga (conditions: pH 4, 95 °C for 10 minutes). FIG. 2A shows labeling test with 100 µg of PSMA-11 and 100 mCi of ^{68}Ga (radiochemical yield = 100%, radiochemical purity = >99%). FIG. 2B shows labeling test with 50 µg of PSMA-11 and 100 mCi of ^{68}Ga (radiochemical yield = 100%, radiochemical purity = >99%). FIG. 2C shows labeling test with 25 µg of PSMA-11 and 100 mCi of ^{68}Ga (radiochemical yield = 100%, radiochemical purity = >99%).

FIGS. 3A-3C show HPLC traces of PSMA-11 labeling tests with cyclotron-produced ^{68}Ga (conditions: pH 4, 95 °C for 10 minutes). FIG. 3A shows labeling test with 10 µg of PSMA-11 and 100 mCi of ^{68}Ga (radiochemical yield = 100%, radiochemical purity = >99%). FIG. 3B shows labeling test with 5 µg of PSMA-11 and 100 mCi of ^{68}Ga (radiochemical yield = 100%, radiochemical purity = >99%). FIG. 3C shows labeling test with 1 µg of PSMA-11 and 100 mCi of ^{68}Ga (radiochemical yield = 74%, radiochemical purity = 38.1%).

FIGS. 4A & 4B show HPLC traces of large-scale labeling tests with DOTA-Oct with cyclotron-produced ^{68}Ga (conditions: 1 Ci ^{68}Ga , 500 µg DOTA-Oct, pH 4.5, 95 °C for 10 minutes). FIG. 4A shows radiochemical yield = 87.4% and radiochemical purity = 62.9% at 0 h; FIG. 4B shows radiochemical purity = 17% at 3 h.

FIGS. 5A-5C show HPLC traces of large-scale labeling tests with PSMA-11 with cyclotron-produced ^{68}Ga (conditions: 0.5 Ci ^{68}Ga , 125 µg PSMA-11, pH 4, 95 °C for 10 minutes). FIG. 5A shows labeling test at 0 h: radiochemical yield = 100%, radiochemical purity = >99%; FIG. 5B shows labeling test at 1 h: radiochemical purity = ~66.6%; FIG. 5C shows labeling test at 3 h: radiochemical purity = ~47.9%.

FIGS. 6A-6C show HPLC traces of DOTA-Oct labeling tests with cyclotron-produced ^{68}Ga (conditions: 0.5 Ci ^{68}Ga , 250 μg DOTA-Oct, 200 mg L-ascorbic acid, pH 4.5, 95 °C for 10 minutes) after 0 h (radiochemical purity = >99%, FIG. 6A), 1 h (radiochemical purity = >99%, FIG. 6B), and 4 h (radiochemical purity = >99%, FIG. 6C).

5 FIGS. 7A-7C show HPLC traces of PSMA-11 labeling tests with cyclotron-produced ^{68}Ga (conditions: 0.5 Ci ^{68}Ga , 125 μg PSMA-11, 200 mg L-ascorbic acid, pH 4, 95 °C for 10 minutes) after 0 h (radiochemical purity = >99%, FIG. 7A), 1 h (radiochemical purity = >99%, FIG. 7B), and 4 h (radiochemical purity = >99%, FIG. 7C).

10 FIGS. 8A & 8B show HPLC traces of PSMA-11 labeling tests with generator-produced ^{68}Ga . FIG. 8A shows the HPLC trace of a standard of ^{68}Ga -PSMA-11. FIG. 8B shows the HPLC trace of PSMA-11 with generator-produced ^{68}Ga (conditions: 0.5 18 mCi ^{68}Ga , 50 μg PSMA-11, pH 4, 95 °C for 10 minutes) and shows radiochemical yield = 100% and radiochemical purity = >99%.

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DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

I. Introduction

Disclosed herein are methods and systems for the rapid purification of ^{68}Ga solutions, compositions comprising ^{68}Ga solutions prepared using said methods and systems, as well as methods of using said compositions to image biological tissues, such as tumors. The methods of purification comprise contacting a solution of ^{68}Ga to be purified with a single anion-exchange resin.

Gallium-68 is a positron-emitting radioisotope that can be produced from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator or from proton beam bombardment of ^{68}Zn in a cyclotron. ^{68}Ga -labeled peptides are a valuable class of radiopharmaceuticals exhibiting fast target localization and blood clearance. ^{68}Ga -DOTATOC, ^{68}Ga -DOTATATE, ^{68}Ga -DOTANOC, are the most prominent radiopharmaceuticals currently in use for imaging and differentiating lesions of various somatostatin receptor subtypes, overexpressed in many neuroendocrine tumors. The number of clinical trials with ^{68}Ga has increased dramatically, including within the United States.

As demand for ^{68}Ga increases for use in radiopharmaceuticals, the need for improved methods for the synthesis and subsequent processing of ^{68}Ga has grown significantly. Current methods for processing ^{68}Ga require multiple purification steps (i.e. passing the crude ^{68}Ga solution through more than one ion-exchange resin) and/or additional concentration and reconstitution steps in order to achieve a purity level and concentration sufficient to radiolabel carrier molecules for administration to patients. Such additional processing steps take time and leads to a lower specific activity of the purified ^{68}Ga as a result of the short half-life of ^{68}Ga (~68 minutes). As such, there is a need for methods that can produce purified ^{68}Ga quickly while removing unwanted impurities such as zinc, iron, and/or germanium.

This invention is based, in part, on the discovery of a fully defined process of preparing purified ^{68}Ga using a single anion-exchange resin which rapidly and directly provides the purified ^{68}Ga in a solution sufficient such that no further processing is required prior to use in radiolabeling. As shown in the Examples, there is provided a method to prepare a purified, carrier-free solution of ^{68}Ga with very high specific activity.

II. Definitions

The use of the word “a” or “an,” when used in conjunction with the term “comprising” in the claims and/or the specification may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one,” and “one or more than one.”

Throughout this application, the term “about” is used to indicate that a value includes the inherent variation of error for the device employed to determine the value, the method being employed to determine the value, or the variation that exists among the study subjects or patients.

The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

When used in the context of a chemical group: “hydrogen” means $-H$; “hydroxy” means $-OH$; “oxo” means $=O$; “carbonyl” means $-C(=O)-$; “carboxy” means $-C(=O)OH$ (also written as $-COOH$ or $-CO_2H$); “halo” means independently $-F$, $-Cl$, $-Br$ or $-I$; “amino” means $-NH_2$; “hydroxyamino” means $-NHOH$; “nitro” means $-NO_2$; imino means $=NH$; “cyano” means $-CN$; “isocyanyl” means $-N=C=O$; “azido” means $-N_3$; in a monovalent context “phosphate” means $-OP(O)(OH)_2$ or a deprotonated form thereof; in a divalent context “phosphate” means $-OP(O)(OH)O-$ or a deprotonated form thereof; “mercapto” means $-SH$; and “thio” means $=S$; “sulfonyl” means $-S(O)_2-$; and “sulfinyl” means $-S(O)-$.

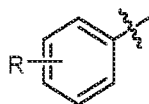
Unless specified otherwise, any chemical group or compound class listed in a claim set has a carbon atom limit of less than or equal to twelve.

In the context of chemical formulas, the symbol “—” means a single bond, “=” means a double bond, and “≡” means triple bond. The symbol “----” represents an optional bond, which if present is either single or double. The symbol “====” represents a single bond or a double bond.

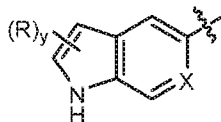
Thus, the formula  covers, for example, , , ,  and . And it is understood that no one such ring atom forms part of more than one double bond. Furthermore, it is noted that the covalent bond symbol “—”, when connecting one or two stereogenic atoms, does not indicate any preferred stereochemistry. Instead, it covers all stereoisomers as well as mixtures thereof. The symbol “”, when drawn perpendicularly across a bond (e.g., -CH₃ for methyl) indicates a point of attachment of the group. It is noted that the point of attachment is typically only identified in this manner for larger groups in order to assist the reader in unambiguously identifying a point of attachment. The symbol “” means a single bond where the group attached to the thick end of the wedge is “out of the page.” The symbol “” means a single bond where the group attached to the thick end of the wedge is “into the page”. The symbol “” means a single bond where the geometry around a double bond (e.g., either *E* or *Z*) is undefined. Both options, as well as combinations thereof are therefore intended. Any undefined valency on an atom of a structure shown in this application implicitly represents a hydrogen atom

bonded to that atom. A bold dot on a carbon atom indicates that the hydrogen attached to that carbon is oriented out of the plane of the paper.

When a variable is depicted as a “floating group” on a ring system, for example, the group “R” in the formula:



then the variable may replace any hydrogen atom attached to any of the ring atoms, including a depicted, implied, or expressly defined hydrogen, so long as a stable structure is formed. When a variable is depicted as a “floating group” on a fused ring system, as for example the group “R” in the formula:



then the variable may replace any hydrogen attached to any of the ring atoms of either of the fused rings unless specified otherwise. Replaceable hydrogens include depicted hydrogens (*e.g.*, the hydrogen attached to the nitrogen in the formula above), implied hydrogens (*e.g.*, a hydrogen of the formula above that is not shown but understood to be present), expressly defined hydrogens, and optional hydrogens whose presence depends on the identity of a ring atom (*e.g.*, a hydrogen attached to group X, when X equals $-\text{CH}-$), so long as a stable structure is formed. In the example depicted, R may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula above, the subscript letter “y” immediately following the R enclosed in parentheses, represents a numeric variable. Unless specified otherwise, this variable can be 0, 1, 2, or any integer greater than 2, only limited by the maximum number of replaceable hydrogen atoms of the ring or ring system.

The term “saturated” when used to modify a compound or chemical group means the compound or chemical group has no carbon-carbon double and no carbon-carbon triple bonds, except as noted below. When the term is used to modify an atom, it means that the atom is not part of any double or triple bond. In the case of substituted versions of saturated groups, one or more carbon oxygen double bond or a carbon nitrogen double bond may be present. And when such a bond is present, then carbon-carbon double bonds that may occur as part of keto-enol tautomerism or imine/enamine tautomerism are not precluded. When the term “saturated” is used to modify a solution of a substance, it means that no more of that substance can dissolve in that solution.

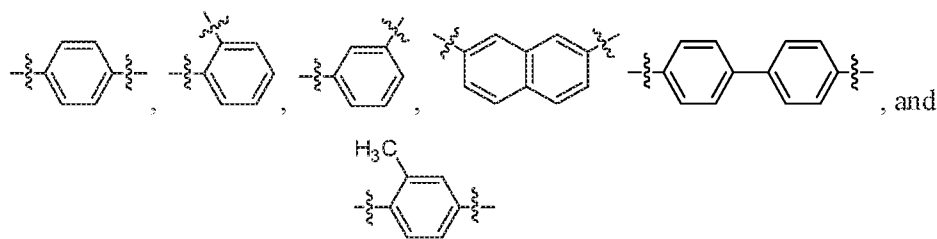
The term “aliphatic” signifies that the compound or chemical group so modified is an acyclic or cyclic, but non-aromatic compound or group. In aliphatic compounds/groups, the carbon atoms can be joined together in straight chains, branched chains, or non-aromatic rings (alicyclic). Aliphatic compounds/groups can be saturated, that is joined by single carbon-carbon bonds (alkanes/alkyl), or unsaturated, with one or more carbon-carbon double bonds (alkenes/alkenyl) or with one or more carbon-carbon triple bonds (alkynes/alkynyl).

The term “aromatic” signifies that the compound or chemical group so modified has a planar unsaturated ring of atoms with $4n + 2$ electrons in a fully conjugated cyclic π system.

The term “alkyl” when used without the “substituted” modifier refers to a monovalent saturated aliphatic group with a carbon atom as the point of attachment, a linear or branched acyclic structure, and no atoms other than carbon and hydrogen. The groups $-\text{CH}_3$ (Me), $-\text{CH}_2\text{CH}_3$ (Et), $-\text{CH}_2\text{CH}_2\text{CH}_3$ (*n*-Pr or propyl), $-\text{CH}(\text{CH}_3)_2$ (*i*-Pr, *i*Pr or isopropyl), $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ (*n*-Bu), $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ (*sec*-butyl), $-\text{CH}_2\text{CH}(\text{CH}_3)_2$ (isobutyl), $-\text{C}(\text{CH}_3)_3$ (*tert*-butyl, *t*-butyl, *t*-Bu or *t*Bu), and $-\text{CH}_2\text{C}(\text{CH}_3)_3$ (*neo*-pentyl) are non-limiting examples of alkyl groups. The term “alkanediyl” when used without the “substituted” modifier refers to a divalent saturated aliphatic group, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The groups $-\text{CH}_2-$ (methylene), $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$, and $-\text{CH}_2\text{CH}_2\text{CH}_2-$ are non-limiting examples of alkanediyl groups. The term “alkylidene” when used without the “substituted” modifier refers to the divalent group $=\text{CRR}'$ in which R and R' are independently hydrogen or alkyl. Non-limiting examples of alkylidene groups include: $=\text{CH}_2$, $=\text{CH}(\text{CH}_2\text{CH}_3)$, and $=\text{C}(\text{CH}_3)_2$. An “alkane” refers to the class of compounds having the formula $\text{H}-\text{R}$, wherein R is alkyl as this term is defined above. When any of these terms is used with the “substituted” modifier, one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or $-\text{S}(\text{O})_2\text{NH}_2$. The following groups are non-limiting examples of substituted alkyl groups: $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, $-\text{CF}_3$, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{C}(\text{O})\text{OH}$, $-\text{CH}_2\text{C}(\text{O})\text{OCH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, and $-\text{CH}_2\text{CH}_2\text{Cl}$.

The term “aryl” when used without the “substituted” modifier refers to a monovalent unsaturated aromatic group with an aromatic carbon atom as the point of attachment, said carbon atom forming part of a one or more aromatic ring structures, each with six ring atoms that are all carbon, and wherein the group consists of no atoms other than carbon and hydrogen. If more than one ring is present, the rings may be fused or unfused. Unfused rings are connected with a covalent

bond. As used herein, the term aryl does not preclude the presence of one or more alkyl groups (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. Non-limiting examples of aryl groups include phenyl (Ph), methylphenyl, (dimethyl)phenyl, $-\text{C}_6\text{H}_4\text{CH}_2\text{CH}_3$ (ethylphenyl), naphthyl, and a monovalent group derived from biphenyl (*e.g.*, 4-phenylphenyl). The term “arenediyl” when used without the “substituted” modifier refers to a divalent aromatic group with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic ring structures, each with six ring atoms that are all carbon, and wherein the divalent group consists of no atoms other than carbon and hydrogen. As used herein, the term arenediyl does not preclude the presence of one or more alkyl groups (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. If more than one ring is present, the rings may be fused or unfused. Unfused rings are connected with a covalent bond. Non-limiting examples of arenediyl groups include:



The term “aralkyl” when used without the “substituted” modifier refers to the monovalent group $-\text{alkanediyl-aryl}$, in which the terms alkanediyl and aryl are each used in a manner consistent with the definitions provided above. Non-limiting examples are: phenylmethyl (benzyl, Bn) and 2-phenyl-ethyl. When the term aralkyl is used with the “substituted” modifier one or more hydrogen atom from the alkanediyl and/or the aryl group has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or $-\text{S}(\text{O})_2\text{NH}_2$. Non-limiting examples of substituted aralkyls are: (3-chlorophenyl)-methyl, and 2-chloro-2-phenyl-eth-1-yl.

The term “phosphonate” when used without the “substituted” modifier refers to a compound with the formula $\text{R-P}(\text{O})(\text{OR}')(\text{OR}'')$, in which R, R', and R'' can be the same or different alkyl, aryl, or aralkyl groups, as those terms are defined above, or R' and R'' can be taken together to represent an alkanediyl. Non-limiting examples of phosphonate include: $\text{Et-P}(\text{O})(\text{OMe})(\text{OBn})$ and $\text{C}_5\text{H}_{11}\text{-P}(\text{O})(\text{OC}_5\text{H}_{11})_2$. When any of these terms is used with the “substituted” modifier, one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$,

$-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or $-\text{S}(\text{O})_2\text{NH}_2$.

In the present specification reference is made to specific isotopes of elements, e.g. gallium-68. Isotopes are designated either with a superscripted mass number prefix or a hyphenated, non-superscripted suffix, e.g. gallium-68 or ^{68}Ga . Isotopes as disclosed herein should not necessarily be taken to refer to the neutral elements but may refer to ions of these isotopes or to complexes thereof. Thus, for example “ ^{68}Ga ” should be taken to refer to a ^{68}Ga species, e.g. $^{68}\text{Ga}^{3+}$ or a ^{68}Ga complex, for example a citrate complex. Such complexes may themselves be neutral or may be electrically charged.

An “excipient” is a pharmaceutically acceptable substance formulated along with the active ingredient(s) of a medication, pharmaceutical composition, formulation, or drug delivery system. Excipients may be used, for example, to stabilize the composition, to bulk up the composition (thus often referred to as “bulking agents,” “fillers,” or “diluent” when used for this purpose), or to confer a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug absorption, reducing viscosity, or enhancing solubility. Excipients include pharmaceutically acceptable versions of antiadherents, binders, coatings, colors, disintegrants, flavors, glidants, lubricants, preservatives, sorbents, sweeteners, and vehicles. The main excipient that serves as a medium for conveying the active ingredient is usually called the vehicle. Excipients may also be used in the manufacturing process, for example, to aid in the handling of the active substance, such as by facilitating powder flowability or non-stick properties, in addition to aiding *in vitro* stability such as prevention of denaturation or aggregation over the expected shelf life. The suitability of an excipient will typically vary depending on the route of administration, the dosage form, the active ingredient, as well as other factors.

As used herein, the term “patient” or “subject” refers to a living mammalian organism, such as a human, monkey, cow, sheep, goat, dog, cat, mouse, rat, guinea pig, or transgenic species thereof. In certain embodiments, the patient or subject is a primate. Non-limiting examples of human patients are adults, juveniles, infants and fetuses.

An “active ingredient” (AI) or active pharmaceutical ingredient (API) (also referred to as an active compound, active substance, active agent, pharmaceutical agent, radiological agent, imaging agent, biologically active molecule, or a therapeutic compound) is the ingredient in a pharmaceutical drug that is biologically or radiologically active.

As generally used herein “pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues, organs, and/or bodily fluids of human beings

and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

A “pharmaceutically acceptable carrier,” “drug carrier,” or simply “carrier” is a pharmaceutically acceptable substance formulated along with the active ingredient that is involved in carrying, delivering and/or transporting a chemical agent. Carriers may be used to improve the delivery and the effectiveness of drugs, including for example, controlled-release technology to modulate drug bioavailability, decrease drug metabolism, and/or reduce drug toxicity. Some carriers may increase the effectiveness of drug delivery to the specific target sites. Some carriers may target specific tissues such as thyroid, brain, gastrointestinal, pancreas, spleen, kidney, neuroendocrine tumors, renal cell carcinoma, lung cancer, breast cancer, prostate cancer, and malignant lymphoma. Non-limiting examples of carriers include: peptides, small molecules, antibodies, or antibody-drug conjugates, or fragments thereof. Further non-limiting examples of carrier molecules include prostate-specific membrane antigen (PSMA), 1,4,7-triazacyclononane-N,N',N''-triacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), diethylene triamine pentaacetic acid (DTPA), desferrioxamine, DOTA-Tyr(3)-octreotide (DOTATOC), DOTA-Tyr(3)-Tyr(8)-octreotide (DOTATATE), DOTA-1-naphthyl-alanine (DOTANOC), DOTA-benzothienyl-alanine (DOTA-BOC), DOTA-bombesin, DOTA-arginine-glycine-aspartic acid-bombesin (DOTA-RGD-bombesin), NOTA-RGD, 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15)-,11,13-triene-3,6,9-triacetic acid-RGD (PCTA-RGD), DOTA-albumin, DOTA-human epidermal growth factor, 1,4,7-triazacyclononane-1-[methyl(2-carboxyethyl)phosphinic acid]-4,7-bis[methyl(2-hydroxymethyl)phosphinic acid]-integrin α (IIb) β (3)-specific cyclic hexapeptide (NOPO-RGDfK), 1,4,7-triazacyclononane-1,4-bis(acetic acid)-7-(2-glutaric acid) (NODAGA), NOPO-Nal(3)-octreotide conjugate (NOPO-NOC), 1,4,7-triazacyclononane-1,4,7-tris[(2-carboxyethyl)methylenephosphinic acid] (TRAP(RGD)₃), or citrate.

A “pharmaceutical drug” (also referred to as a pharmaceutical, pharmaceutical preparation, pharmaceutical composition, pharmaceutical formulation, pharmaceutical product, medicinal product, medicine, medication, medicament, or simply a drug, agent, or preparation) is a composition used to diagnose, image, cure, treat, or prevent disease, which comprises an active pharmaceutical ingredient (API) (defined above) and optionally contains one or more inactive ingredients, which are also referred to as excipients (defined above).

“Prevention” or “preventing” includes: (1) inhibiting the onset of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or

display any or all of the pathology or symptomatology of the disease, and/or (2) slowing the onset of the pathology or symptomatology of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease.

5 “Treatment” or “treating” includes (1) inhibiting a disease in a subject or patient experiencing or displaying the pathology or symptomatology of the disease (*e.g.*, arresting further development of the pathology and/or symptomatology), (2) ameliorating a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease (*e.g.*, reversing the pathology and/or symptomatology), and/or (3) effecting any measurable decrease in
10 a disease or symptom thereof in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease.

 The term “unit dose” refers to a formulation of the compound or composition such that the formulation is prepared in a manner sufficient to provide a single therapeutically effective dose of the active ingredient to a patient in a single administration. Such unit dose formulations that may
15 be used include but are not limited to a single tablet, capsule, or other oral formulations, or a single vial with a syringeable liquid or other injectable formulations.

 The above definitions supersede any conflicting definition in any reference that is incorporated by reference herein. The fact that certain terms are defined, however, should not be considered as indicative that any term that is undefined is indefinite. Rather, all terms used are
20 believed to describe the invention in terms such that one of ordinary skill can appreciate the scope and practice the present invention.

III. Production of Gallium-68 to be Purified

 In the first step of the method provided herein for preparing a purified, carrier-free ^{68}Ga solution, a ^{68}Ga solution comprising ^{68}Ga to be purified is obtained. The ^{68}Ga solution comprising
25 ^{68}Ga to be purified may be prepared through, or a byproduct of, the synthesis of ^{68}Ga . The ^{68}Ga to be purified may be synthesized using a cyclotron. A cyclotron is understood to be an apparatus in which charged atomic and subatomic particles are accelerated by an alternating electric field while following an outward spiral or circular path in a magnetic field. Without wishing to be bound by any theory, the ^{68}Ga to be purified is synthesized via irradiation of a metal sample
30 comprising ^{68}Zn , which upon irradiation is converted into ^{68}Ga . The metal sample may be in the form of a liquid target or in the form of a solid target, *e.g.* a solution of ZnNO_2 or solid ^{68}Zn . When a liquid target is employed, the ^{68}Zn is dissolved and the liquid target may further comprise an acidic solution. When a solid target is employed, the solid target may be suspended in an acidic solution or an acidic solution may be added upon or after irradiation. The acidic solution may

comprise HCl or an acid derived from the dissociation of HCl. Such acids are understood to be the protonated form of a solvent, e.g. H_3O^+ in the case of water as a solvent or CH_3OH_2^+ in the case of methanol as a solvent. The acid may have a concentration of about 0.1, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 N. The ^{68}Ga solution comprising ^{68}Ga to be purified may be an aqueous solution.

5 IV. Purification of Gallium-68

In another step, the ^{68}Ga solution comprising ^{68}Ga to be purified is contacted with an anion-exchange resin. The anion-exchange resin may be treated with an acidic solution prior to contacting the resin with the ^{68}Ga solution comprising ^{68}Ga to be purified. The anion-exchange resin should have a higher affinity for ^{68}Ga than for zinc, iron, germanium or other impurities so
10 that the impurities are eluted from the anion-exchange resin while the majority, preferably substantially all, of the ^{68}Ga is retained on the anion-exchange resin under an initial set of conditions. The anion-exchange resin should have an affinity for ^{68}Ga that can be modulated so as to allow for the ^{68}Ga to be eluted from the resin under a second set of conditions. The anion-exchange resin may comprise an amine group or phosphonate, e.g. phosphonate, such as the
15 UTEVA[®] resin. The resin should be resistant to radiation. The methods and systems disclosed herein employ a single anion-exchange resin. Whereas other methods employ a single cation-exchange resin or a combination of two different ion-exchange resins, the methods disclosed herein comprise a single anion-exchange resin. Use of a single anion-exchange resin reduces the amount of time required to purify ^{68}Ga and provides ^{68}Ga with a higher specific activity.
20 Commonly, the anion-exchange resins are in particulate form, so that a resin column contains a packed bed of the particulate resin. The resin may be porous, e.g. microporous, mesoporous, nanoporous etc. A typical resin column may contain from about 0.01 g to about 2 g of resin, e.g. about 0.01, 0.05, 0.1, 0.15, 0.2, 0.3, 0.4, 0.5, 1, 1.5, or 2 g.

After contacting the anion-exchange resin with the ^{68}Ga solution comprising ^{68}Ga to be
25 purified, the resin may be optionally washed with a washing solution. The washing solution may comprise an acid, including but not limited to HCl, or an acid derived from the dissociation of the acid, e.g. H_3O^+ . The acid of the washing solution may have a concentration of greater than 1 N, such as from about 2 N to 8 N, e.g. 2 N, 3 N, 4 N, 5 N, 6 N, 7 N, or 8 N. The washing solution may be an aqueous solution.

30 Following the optional washing step, ^{68}Ga is eluted from the anion-exchange resin by contacting the anion-exchange resin with an eluting solution. Without wishing to be bound by theory, the eluting solution modulates the affinity of the anion-exchange resin for ^{68}Ga . The eluting solution may comprise an acid, including but not limited to HCl, or an acid derived from the dissociation of the acid, e.g. H_3O^+ . The acid of the eluting solution may have a concentration

of from about 0.005 N to about 2 N, e.g. 0.005 N, 0.01 N, 0.02 N, 0.03 N, 0.04 N, 0.05 N, 0.06 N, 0.07 N, 0.08 N, 0.09 N, 0.1 M, 0.5 N, 1 N, or 2 N. The eluting solution may be an aqueous solution.

The resulting purified, carrier-free ^{68}Ga solution has a specific activity of greater than about 25 GBq/ μg . The specific activity may be from about 25 GBq/ μg to about 100,000 GBq/ μg , e.g. 25, 100, 500, 1000, 10,000, 15,000, 20,000, 25,000, 30,000, 31,000, 32,000, 33,000, 33,100, 33,200, 33,300, 33,400, 33,500, 33,600, 33,700, 33,800, 33,900, 34,000, 35,000, 36,000, 37,000, 38,000, 39,000, 40,000, 50,000, 60,000, 70,000, 80,000, 90,000, or 100,000 GBq/ μg . Specific activity values present in this disclosure are correlated to the End of Bombardment (EOB) unless explicitly noted otherwise.

The present disclosure also provides systems for preparing a purified, carrier-free ^{68}Ga solution. These systems comprise a solid target comprising ^{68}Zn , a cyclotron, wherein the solid target is irradiated using the cyclotron, and a single anion-exchange resin. The system may be portable or may be fixed in a specific location.

V. Compositions of Gallium-68 for Imaging

The present disclosure also provides compositions comprising the purified, carrier-free solution of ^{68}Ga . Compositions may further comprise a carrier molecule. The compositions disclosed herein may be useful for biological imaging, e.g. PET imaging. Compositions may be prepared by the addition of the purified, carrier-free solution of ^{68}Ga to a carrier molecule or a solution comprising a carrier molecule. Further processing of the composition may be performed prior to administration to a patient. Such processing may include purification, concentration, or dilution. Compositions of the present disclosure may also comprise pharmaceutically acceptable excipients.

The compositions disclosed herein may be formulated for administration intraarterially, intraarticularly, intracranially, intrapericardially, intraperitoneally, intratumorally, intravenously, intravesicularly, parenterally, via injection, via local delivery, or via localized perfusion. The compositions may be administered once or more than once. The compositions may be used to image tissue, such as a tumor, e.g. a prostate, pancreatic, lung, or neuroendocrine tumor. The compositions may be used to image a tumor that exhibits elevated levels of PSMA.

VI. Examples

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice.

However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1: Synthesis, Purification, and Analysis of ^{68}Ga

5 All reagents and solvents were purchased from commercial vendors and used directly unless otherwise noted. Enriched ^{68}Zn metal powder (99+% purity) was purchased from ISOFLEX USA (San Francisco, CA). Milli-Q water (18 M Ω ·cm) was obtained from a Millipore Milli-Q Integral 5 water purification system (Billerica, MA). The ITG $^{68}\text{Ge}/^{68}\text{Ga}$ Generator (GMP) was obtained from RadioMedix (Houston, TX). UTEVA[®] resin (50–100 μm) was
10 purchased from Eichrom (Lisle, IL). Hydrochloric acid (33% min., 99.999999% metal basis) was obtained from Alfa Aesar (Pittsburgh, PA) and was diluted to 10 N, 4 N, and 0.05 N with Milli-Q water. 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) was purchased from Sigma-Aldrich (St. Louis, MO). Instant thin-layer chromatography paper (iTLC-SG) was acquired from Fisher Scientific (Hampton, NH). The labeling efficiency of ^{68}Ga -DOTA was determined
15 using radio-TLC with the mobile phase composed of 10% ammonium acetate and methanol in one-to-one ratio. The radio-TLC plates were scanned using a Bioscan AR-2000 radio-TLC scanner (Washington, DC).

The Cyclotron Radiochemistry Facility (CRF) is equipped with a 16.5 MeV proton energy cyclotron (PETtrace, GE Healthcare, Waukesha, WI). Prior to irradiation, a 7 mm diameter of
20 enriched ^{68}Zn (60–120 mg) was electrodeposited on a platinum disc using a solution comprised of $^{68}\text{ZnCl}_2$ and 0.05 N HCl (concentration of ^{68}Zn : 25–30 mg/mL) and a current density of 25 mA/cm². The target was then transferred and mounted in the PETtrace cyclotron through the Comacer EDS/PTS module (Castel Bolognese RA, Italy). The target was irradiated at an incident proton-beam energy of 14.5 MeV with beam currents of 15–40 μA . After irradiation, the target
25 was pneumatically retrieved. Chemical separation of ^{68}Ga was performed and labeling procedures were conducted using the Comacer EDS and GE Healthcare TRACERlab FX modules.

Gallium-68 was separated from ^{68}Zn using a column containing 100 mg of UTEVA[®] resin, in which the resin was pre-conditioned with 10 mL of 6 N HCl. Upon retrieving the irradiated
30 ^{68}Zn target from the cyclotron into the Comacer EDS module, the target was completely dissolved with 10 mL of 6 N HCl under 10 min. The crude $^{68}\text{Ga}/^{68}\text{Zn}$ solution was passed through the column containing the UTEVA[®] resin. After rinsing the transfer lines in the EDS module with 5 mL of 6 N HCl, the HCl rinse was also passed through the column followed by 40 mL of 4 N HCl to remove residual ^{68}Zn and any additional metal contaminants. The [^{68}Ga] GaCl_3 was desorbed

from the resin with 2 mL of 0.05 N HCl and readily available to be used in a labeling reaction without any further processing.

The effective specific activity (GBq/ μ mol) of [^{68}Ga]GaCl₃ was determined through a series of labeling reactions with a chelating solution. Since DOTA is one of the chelators that is often conjugated to a biomolecule for labeling with ^{68}Ga , multiple dilutions of DOTA solution ($2.48 \times 10^{-5} - 2.48 \times 10^2 \mu\text{M}$) in 0.5 M acetate buffer (pH 4.5) were used for the study. A volume of 5 μL ($\sim 74 \text{ MBq}$) of [^{68}Ga]GaCl₃ was first diluted with 1 mL of 0.05 M HCl as a stock solution. The study was performed by adding 50 μL of [^{68}Ga]GaCl₃ stock solution into 200 μL of DOTA solution. The reactions were allowed to precede at 95 °C for 20 min. After incubation was completed, the effective specific activity was determined by measuring labeling efficiency using radio-TLC analysis (mobile phase: 10% ammonium acetate/methanol, 1:1 (v/v)).

Samples containing activities of 0.5–1.0 μCi (18.5–37 KBq) of [^{68}Ga]GaCl₃ in 2 mL microcentrifuge tubes were diluted with Milli-Q water to bring the final volume to 1 mL. The radionuclidic purity was then determined by gamma-ray spectroscopy using a cryogenically cooled germanium (HPGe) detector (ORTEC, Oak Ridge, TN). Samples were counted for 1 h starting immediately after End of Synthesis (EOS) and the measurement was repeated after 24 h. The radionuclidic purity of ^{68}Ga was based on the analysis of the regions of interest (ROI) at EOS and of decayed samples.

ICP-MS analysis of the ^{68}Ga samples, after decay, were conducted at the University of Missouri Research Reactor (MURR). All samples were analyzed on a PerkinElmer NexION 300X ICP-MS operated in kinetic energy discrimination (KED) mode with two different helium cell gas flows at 2.5 and 4.5 mL/min. The amount of gallium, germanium, iron, and zinc in each sample were determined.

Example 2: Evaluation of Cyclotron Irradiated ^{68}Zn Targets and ^{68}Ga Separation and ICP-MS Analysis

Due to the unique characteristics and availability of $^{68}\text{Ge}/^{68}\text{Ga}$ generators, several efforts have been made to translate ^{68}Ga -labeled compounds from preclinical evaluations into routine clinical practice (Amor-Coarasa et al., 2016; Velikyan, 2015; Vis et al., 2015). In order to satisfy the increasing demand for ^{68}Ga in preclinical and clinical applications, an approach to reliably produce ^{68}Ga via $^{68}\text{Zn}(p,n)^{68}\text{Ga}$ reaction in significantly large quantities was investigated. The methods described herein have been used successfully for the cyclotron production and chemical separation of ^{68}Ga . See Table 1 for a comparison of ^{68}Ga production at various facilities.

Table 1. Comparison of ^{68}Ga Production at Various Facilities

z	MDACC ¹	Mayo Clinic/GE ²	University of Coimbra/IBA ³
Target forms	Solid	Liquid	Liquid
Amount of ^{68}Zn	80 mg	200 mg	200 mg
Beam energy	14.5 MeV	14 MeV	14.2 MeV
Production yield at EOB	$2.72 \pm 0.08 \text{ GBq}/\mu\text{g}\cdot\text{h}$	$0.9 \pm 0.01 \text{ GBq}/\mu\text{g}\cdot\text{h}$	$0.3 \text{ GBq}/\mu\text{g}\cdot\text{h}$
Optimized ^{68}Ga processing	Yes (1 column processing)	No	Yes (3 column processing)

¹Lin et al., 2018; ²Pandey et al., 2014; ³Alvesa et al., 2017.

Due to the relatively low melting point of Zn metal (419.5 °C), initial tests with natZn targets were conducted for short time intervals (5 min) at an incident proton-beam energy of 14.5 MeV while increasing beam currents from 15 to 40 μA . No significant heat effects on the electrodeposited natZn were observed throughout the tests indicating efficient heat removal from the target by the EDS/PTS module cooling system. To ensure production reliability during long irradiations targets were tested with beam currents up to 40 μA . No visible heat effects or loss of yield was observed. All subsequent measurements reported here were conducted at a beam current of 30 μA . To optimize target thickness for maximum yield, targets with a diameter of 7 mm and a mass of ^{68}Zn between 60 and 120 mg were bombarded for 20–90 min. The ^{68}Ga activity at End of Bombardment (EOB) correlated well with irradiation time and amount of ^{68}Zn metal present. Targets containing $(104.1 \pm 2.7) \text{ mg } ^{68}\text{Zn}$ ($n = 3$) irradiated for 1 h at a beam current of 30 μA resulted in $60.9 \pm 1.8 \text{ GBq}$ ($1645 \pm 51 \text{ mCi}$) of ^{68}Ga at EOB. The production yield was found to be $2.72 \pm 0.08 \text{ GBq}/\mu\text{A}\cdot\text{h}$ ($73.5 \pm 2.3 \text{ mCi}/\mu\text{A}\cdot\text{h}$). Sadeghi et al. reported production of ^{68}Ga using a 6° grazing incidence target geometry with a proton-beam energy of 15.0 MeV and a beam current of 150 μA (Sadeghi et al., 2009). They report a production yield for a target mass of 434 mg of $5.03 \text{ GBq}/\mu\text{A}\cdot\text{h}$ ($136 \text{ mCi}/\mu\text{A}\cdot\text{h}$) at EOB for a short 15 min irradiation. Their result is not far from the calculated value of $5.81 \text{ GBq}/\mu\text{A}\cdot\text{h}$ ($157 \text{ mCi}/\mu\text{A}\cdot\text{h}$) presented by Szelecsényi et al. derived from cross section measurements (Szelecsényi et al., 2012). These results compare well with these reported values taking into account the lower incident proton-energy employed herein to minimize ^{67}Ga impurities and a reduced target density of $(4.8 \pm 0.4) \text{ g}/\text{cm}^3$ based on target thickness measurements.

During initial development the time required to dissolve the irradiated ^{68}Zn target was investigated. The target was dissolved using 10 mL of 10 N HCl. The completion of the

dissolution process was monitored using the flow meter integrated into the system. At the beginning of the dissolution process hydrogen gas was released partially interrupting the overall flow rate of circulating HCl solution. Once the target was completely dissolved and no more hydrogen gas was being released, the flow rate was re-stabilized. Based on these observations (and posterior verification) we found the total dissolution time required was less than 5 min. High zinc and HCl acid contents in the final ^{68}Ga solution are two potential challenges for cyclotron-produced ^{68}Ga . Although previous reports indicate that most ^{68}Zn can be removed by using the AG[®] 50W cation resin alone (Engle et al., 2012; Pandey et al., 2014), lower specific activity is obtained as it takes a relatively long time (i.e., usually more than an hour) to evaporate the ^{68}Ga solution and reconstitute it with a low concentration of HCl for radiolabeling use. McAlister and Horwitz have established a two-column system which utilizes AG[®] 50W cation resin and UTEVA[®] anion resin to minimize ^{68}Ge breakthrough from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator (McAlister and Philip Horwitz, 2009). However, the two-column system again results in lower specific activity due to processing times. By adapting this concept for processing ^{68}Ga from an irradiated ^{68}Zn target, over 75% of ^{68}Ga produced activity (decay corrected) can be recovered while the cyclotron-produced ^{68}Ga solution results in lower ($p < 0.01$) zinc content (0.004 ± 0.002 $\mu\text{g}/\text{GBq}$) when compared to that of generator-produced ^{68}Ga (0.37 ± 0.09 $\mu\text{g}/\text{GBq}$) after ICP-MS analysis. In addition, low iron content was observed in both cyclotron and generator-produced ^{68}Ga . The germanium was below detection limits for cyclotron-produced ^{68}Ga (See Table 2). It was found that the UTEVA[®] anion-exchange resin could be used to generate ^{68}Ga solutions with high purity and very high specific activity without the need for additional processing. All of these data suggest that the method presented herein not only minimizes zinc and other metal impurities, but also allows the reconstitution of the final ^{68}Ga solution in a low concentration of HCl as well. The whole separation process only takes less than 10 min, which is especially important for ^{68}Ga production.

Table 2. Comparison of Generator- vs. Cyclotron-Produced ^{68}Ga

	Generator-produced $^{68}\text{Ga}^a$	Cyclotron-produced $^{68}\text{Ga}^b$
Effective Specific Activity (GBq/ μmol)	7.06 ± 1.61	6.74 ± 0.83
Absolute Specific Activity (GBq/ μg) ^c	$\sim 2,500$	$\sim 25,000^d$
Zn residue ($\mu\text{g}/\text{GBq}$)	0.37 ± 0.09	0.004 ± 0.002
Fe residue ($\mu\text{g}/\text{GBq}$)	0.12 ± 0.03	0.11 ± 0.07
Ge residue ($\mu\text{g}/\text{GBq}$)	0.0013 ± 0.0001	Less than 0.0001
Isotope Impurities	^{68}Ge ($T_{1/2}$: 271 d), less than 0.005%	^{67}Ga ($T_{1/2}$: 3.3 d), less than 0.3%
Activity Acquired	Up to 40-45 mCi/elution	~ 1.0 Ci at EOB with 1 h irradiation
^{68}Ga Processing Time After Irradiation	N/A	Less than 30 min
Cost	60,000 USD/12 month	Less than 200 USD/batch without ^{68}Zn recovery

^aGenerator-produced ^{68}Ga was purified via two-column method, employing AG[®] 50W and UTEVA[®] columns; ^bCyclotron-produced ^{68}Ga was purified with a single UTEVA[®] column. ^cCorrelated to End of Synthesis. ^dValue correlated to End of Bombardment is $\sim 33,500$ GBq/ μg .

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The effective specific activity of cyclotron and generator-produced ^{68}Ga was determined by DOTA titration using radio-TLC. While the ^{68}Ga -DOTA radio-peak migrates to the solvent front, the unreacted [^{68}Ga] GaCl_3 remains at the origin. In all experiments ($n = 3$ for each study), the effective specific activity of cyclotron and generator-produced [^{68}Ga] GaCl_3 was found to be 6.7 ± 0.8 and 7.1 ± 1.6 GBq/ μmol , respectively. No statistically significant difference ($p = 0.775$) was found in the effective specific activity between cyclotron and generator-produced ^{68}Ga . To confirm the radionuclidic purity of the ^{68}Ga solution produced via the $^{68}\text{Zn}(p,n)^{68}\text{Ga}$ reaction, gamma-ray spectroscopy was performed. A small fraction ($\leq 0.2\%$) of ^{67}Ga was observed when the target was irradiated up to 90 min with 14.5 MeV protons.

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* * * * *

All of the compounds, systems, compositions, and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the disclosure may have focused on several embodiments or may have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations and
5 modifications may be applied to the compounds, compositions, and methods without departing from the spirit, scope, and concept of the invention. All variations and modifications apparent to those skilled in the art are deemed to be within the spirit, scope, and concept of the invention as defined by the appended claims.

10

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CLAIMS

WHAT IS CLAIMED IS:

1. A method of preparing a purified, carrier-free ^{68}Ga solution comprising:
 - a) obtaining a ^{68}Ga solution to be purified comprising ^{68}Ga ;
 - b) contacting the ^{68}Ga solution with an anion-exchange resin; and
 - c) eluting the ^{68}Ga from the anion-exchange resin to obtain the purified, carrier-free ^{68}Ga solution.
2. The method of claim 1, wherein the method comprises contacting the ^{68}Ga solution to be purified with a single anion-exchange resin.
3. The method of claim 1 or claim 2, wherein the method does not comprise contacting the ^{68}Ga solution to be purified or the purified, carrier-free ^{68}Ga solution with another ion-exchange resin.
4. The method of claim 1, wherein the ^{68}Ga in the ^{68}Ga solution to be purified is prepared by synthesizing the ^{68}Ga in the ^{68}Ga solution.
5. The method of claim 4, wherein a cyclotron is used to synthesize the ^{68}Ga .
6. The method of claim 5, wherein the cyclotron comprises a metal sample in the form of a liquid target.
7. The method of claim 6, wherein the metal sample comprises $^{68}\text{Zn}^{2+}$.
8. The method of claim 5, wherein the cyclotron comprises a metal sample in the form of a solid target.
9. The method of claim 8, wherein the metal sample comprises ^{68}Zn .
10. The method according to any one of claims 1-9, wherein the ^{68}Ga solution to be purified comprises an acid.
11. The method of claim 10, wherein the acid has a concentration of greater than about 2 N.
12. The method of claim 11, wherein the acid has a concentration of from about 3 N to about 10 N.
13. The method of claim 12, wherein the acid has a concentration of about 6 N.
14. The method according to any one of claims 10-13, wherein the acid is HCl or is derived from the dissociation of HCl.

15. The method according to any one of claims 1-14, wherein the ^{68}Ga solution to be purified is an aqueous solution.
16. The method according to any one of claims 1-15, wherein the anion-exchange resin comprises a phosphonate or a substituted phosphonate.
17. The method of claim 16, wherein the anion-exchange resin comprises a phosphonate.
18. The method of claim 17, wherein the anion-exchange resin comprises dipentyl pentylphosphonate.
19. The method according to any one of claims 1-18, wherein the method further comprises washing the anion-exchange resin with a washing solution.
20. The method of claim 19, wherein the washing step occurs before the eluting step.
21. The method of claim 19, wherein the washing solution comprises an acid.
22. The method of claim 21, wherein the acid has a concentration of greater than about 1 N.
23. The method of claim 22, wherein the acid has a concentration of from about 2 N to about 8 N.
24. The method of claim 23, wherein the acid has a concentration of about 4 N.
25. The method according to any one of claims 21-24, wherein the acid is HCl or is derived from the dissociation of HCl.
26. The method according to any one of claims 19 and 21-25, wherein the washing solution is an aqueous solution.
27. The method according to any one of claims 1-26, wherein eluting comprises contacting the anion-exchange resin with an eluting solution.
28. The method of claim 27, wherein the eluting solution comprises an acid.
29. The method of claim 28, wherein the acid has a concentration of from about 0.005 N to about 2 N.
30. The method of claim 29, wherein the acid has a concentration from about 0.01 N to about 1 N.
31. The method of claim 30, wherein the acid has a concentration of about 0.05 N.
32. The method according to any one of claims 28-31, wherein the acid is HCl or is derived from the dissociation of HCl.

33. The method according to any one of claims 27-32, wherein the eluting solution is an aqueous solution.
34. The method according to any one of claims 1-33, wherein the purified, carrier-free ^{68}Ga solution has an activity of from about 37 MBq to about 370 GBq.
35. The method of claim 34, wherein the purified, carrier-free ^{68}Ga solution has an activity of from about 370 MBq to about 370 GBq.
36. The method of claim 35, wherein the purified, carrier-free ^{68}Ga solution has an activity of from about 3.7 GBq to about 370 GBq.
37. The method according to any one of claims 1-36, wherein the purified, carrier-free ^{68}Ga solution comprises less than about 1 $\mu\text{g}/\text{GBq}$ of zinc.
38. The method of claim 37, wherein the purified, carrier-free ^{68}Ga solution comprises less than about 0.1 $\mu\text{g}/\text{GBq}$ of zinc.
39. The method of claim 38, wherein the purified, carrier-free ^{68}Ga solution comprises less than about 0.01 $\mu\text{g}/\text{GBq}$ of zinc.
40. The method according to any one of claims 1-39, wherein the purified, carrier-free ^{68}Ga solution comprises less than about 10 $\mu\text{g}/\text{GBq}$ of iron.
41. The method of claim 40, wherein the purified, carrier-free ^{68}Ga solution comprises less than about 1 $\mu\text{g}/\text{GBq}$ of iron.
42. The method of claim 41, wherein the purified, carrier-free ^{68}Ga solution comprises less than about 0.5 $\mu\text{g}/\text{GBq}$ of iron.
43. The method according to any one of claims 1-42, wherein the purified, carrier-free ^{68}Ga solution comprises less than about 1 $\mu\text{g}/\text{GBq}$ of germanium.
44. The method of claim 43, wherein the purified, carrier-free ^{68}Ga solution comprises less than about 0.01 $\mu\text{g}/\text{GBq}$ of germanium.
45. The method of claim 44, wherein the purified, carrier-free ^{68}Ga solution comprises less than about 0.0001 $\mu\text{g}/\text{GBq}$ of germanium.
46. The method according to any one of claims 1-45, wherein the purified, carrier-free ^{68}Ga solution has a specific activity of greater than about 25 GBq/ μg .
47. The method of claim 46, wherein the purified, carrier-free ^{68}Ga solution has a specific activity of from about 25 GBq/ μg to about 100,000 GBq/ μg .

48. The method of claim 47, wherein the purified, carrier-free ^{68}Ga solution has a specific activity of from about 100 GBq/ μg to about 100,000 GBq/ μg .
49. The method of claim 48, wherein the purified, carrier-free ^{68}Ga solution has a specific activity of from about 1,000 GBq/ μg to about 100,000 GBq/ μg .
50. The method of claim 49, wherein the purified, carrier-free ^{68}Ga solution has a specific activity of from about 10,000 GBq/ μg to about 80,000 GBq/ μg .
51. The method of claim 50, wherein the purified, carrier-free ^{68}Ga solution has a specific activity of from about 25,000 GBq/ μg to about 50,000 GBq/ μg .
52. The method of claim 51, wherein the purified, carrier-free ^{68}Ga solution has a specific activity of from about 31,000 GBq/ μg to about 36,000 GBq/ μg .
53. A purified, carrier-free ^{68}Ga solution prepared according to any one of claims 1-52.
54. A system for preparing a purified, carrier-free ^{68}Ga solution comprising:
 - a) a solid target comprising ^{68}Zn ;
 - b) a cyclotron, wherein the solid target is irradiated using the cyclotron; and
 - c) an anion-exchange resin.
55. The system of claim 54, wherein the system comprises a single anion-exchange resin.
56. The system of claim 54 or claim 55, wherein the system does not comprise another ion-exchange resin.
57. The system of claim 54, wherein the anion-exchange resin comprises a phosphonate or a substituted phosphonate.
58. The system of claim 54, wherein the anion-exchange resin comprises a phosphonate.
59. The system of claim 58, wherein the anion-exchange resin comprises dipentyl pentylphosphonate.
60. The system according to any one of claims 54-59, wherein the purified, carrier-free ^{68}Ga solution has a specific activity of from about 25 GBq/ μg to about 100,000 GBq/ μg .
61. The system of claim 60, wherein the purified, carrier-free ^{68}Ga solution has a specific activity of from about 100 GBq/ μg to about 100,000 GBq/ μg .
62. The system of claim 61, wherein the purified, carrier-free ^{68}Ga solution has a specific activity of from about 1,000 GBq/ μg to about 100,000 GBq/ μg .

63. The system of claim 62, wherein the purified, carrier-free ^{68}Ga solution has a specific activity of from about 10,000 GBq/ μg to about 85,000 GBq/ μg .
64. The system of claim 63, wherein the purified, carrier-free ^{68}Ga solution has a specific activity of from about 25,000 GBq/ μg to about 50,000 GBq/ μg .
65. The method of claim 64, wherein the purified, carrier-free ^{68}Ga solution has a specific activity of from about 31,000 GBq/ μg to about 36,000 GBq/ μg .
66. A composition comprising the purified, carrier-free ^{68}Ga solution of claim 53.
67. The composition of claim 66, wherein the composition further comprises a carrier molecule, wherein the carrier molecule is radiolabeled with the ^{68}Ga of the purified, carrier-free ^{68}Ga solution.
68. The composition of claim 67, wherein the carrier molecule is an antibody or a fragment thereof.
69. The composition of claim 67, wherein the carrier molecule is a peptide or a fragment thereof.
70. The composition of claim 67, wherein the carrier molecule is prostate-specific membrane antigen (PSMA), 1,4,7-triazacyclononane- $\text{N},\text{N}',\text{N}''$ -triacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), diethylene triamine pentaacetic acid (DTPA), desferrioxamine, DOTA-Tyr(3)-octreotide (DOTATOC), DOTA-Tyr(3)-Tyr(8)-octreotide (DOTATATE), DOTA-1-naphthyl-alanine (DOTANOC), DOTA-benzothienyl-alanine (DOTA-BOC), DOTA-bombesin, DOTA-arginine-glycine-aspartic acid-bombesin (DOTA-RGD-bombesin), NOTA-RGD, 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15)-,11,13-triene-3,6,9-triacetic acid-RGD (PCTA-RGD), DOTA-albumin, DOTA-human epidermal growth factor, 1,4,7-triazacyclononane-1-[methyl(2-carboxyethyl)phosphinic acid]-4,7-bis[methyl(2-hydroxymethyl)phosphinic acid]-integrin $\alpha(\text{IIb})\beta(3)$ -specific cyclic hexapeptide (NOPO-RGDfK), 1,4,7-triazacyclononane-1,4-bis(acetic acid)-7-(2-glutaric acid) (NODAGA), NOPO-NaI(3)-octreotide conjugate (NOPO-NOC), 1,4,7-triazacyclononane-1,4,7-tris[(2-carboxyethyl)methylenephosphinic acid] (TRAP(RGD)₃), or citrate.
71. The composition of claim 70, wherein the carrier molecule is PSMA, DOTATATE, DOTATOC, DOTANOC, or citrate.
72. The composition of claim 71, wherein the carrier molecule is PSMA.

73. The composition of claim 71, wherein the carrier molecule is DOTATATE.
74. The composition of claim 71, wherein the carrier molecule is citrate.
75. The composition according to any one of claims 67-74, wherein the carrier molecule targets a human tissue.
76. The composition of claim 75, wherein the human tissue is selected from the following: thyroid, brain, gastrointestinal, pancreas, spleen, kidney, neuroendocrine tumors, renal cell carcinoma, lung cancer, breast cancer, prostate cancer, and malignant lymphoma.
77. A method of imaging comprising administering a composition according to any one of claims 66-76 to a patient.
78. The method of claim 77, wherein the patient is a mammal.
79. The method of claim 78, wherein the mammal is a human.
80. The method according to any one of claims 77-79, wherein the composition is administered more than once.
81. The method according to any one of claims 77-79, wherein the composition is administered once.
82. The method according to any one of claims 77-81, wherein the composition is formulated for administration intraarterially, intraarticularly, intracranially, intrapericardially, intraperitoneally, intratumorally, intravenously, intravesicularly, parenterally, via injection, via local delivery, or via localized perfusion.
83. The method of claim 82, wherein the composition is formulated for administration intravenously.
84. The method according to any one of claims 77-83, wherein the composition is formulated as a unit dose.
85. The method according to any one of claims 77-84, wherein the method further comprises imaging a tumor.
86. The method of claim 85, wherein the tumor is a neuroendocrine tumor.
87. The method of claim 85, wherein the tumor expresses elevated levels of PSMA.
88. The method according to any one of claims 85-87, wherein the tumor is a pancreatic tumor, a prostate tumor, or a lung tumor.
89. The method of claim 88, wherein the tumor is a pancreatic tumor.

90. The method of claim 88, wherein the tumor is a prostate tumor.
91. The method of claim 88, wherein the tumor is a lung tumor.

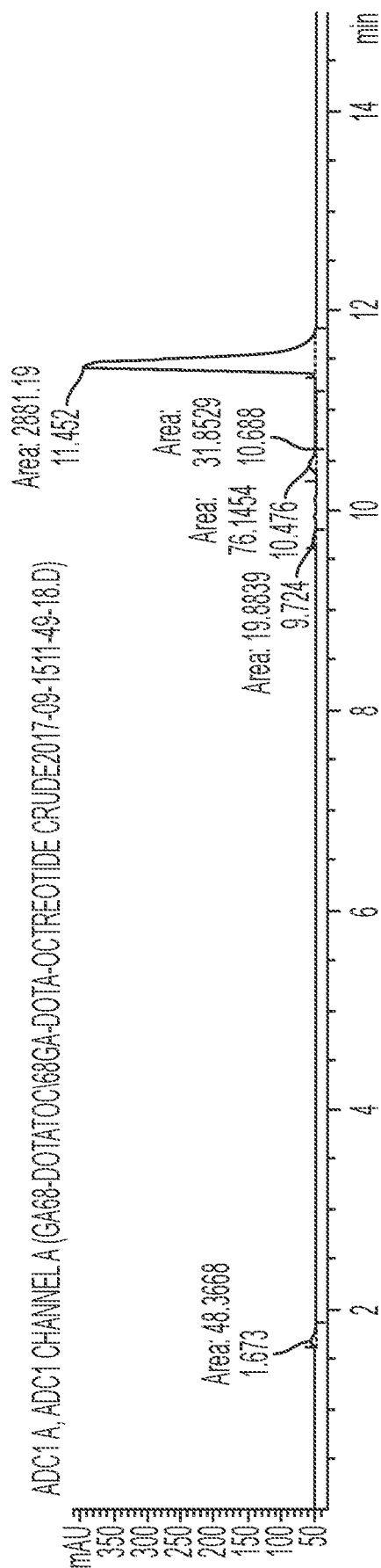


FIG. 1A

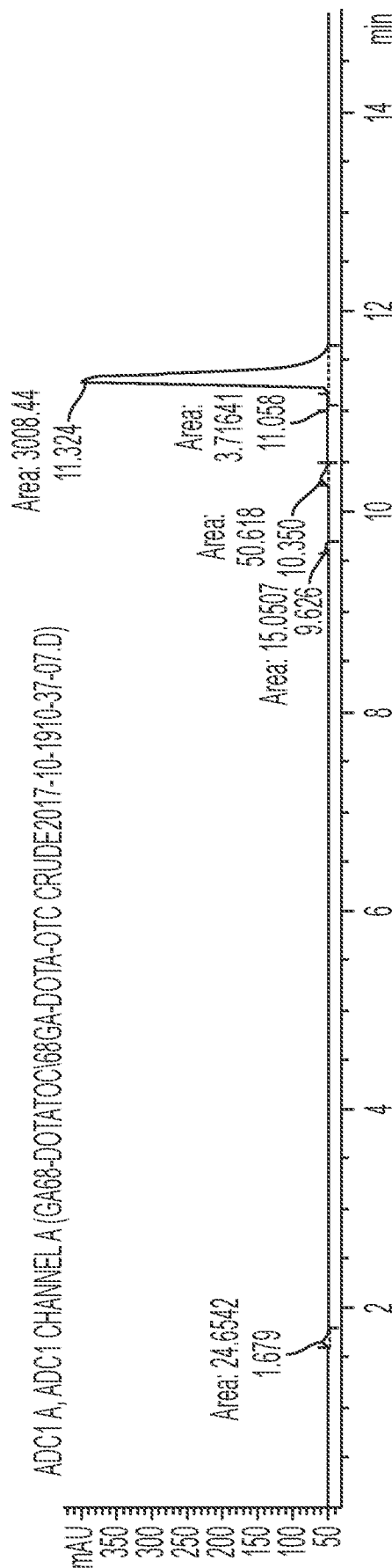


FIG. 1B

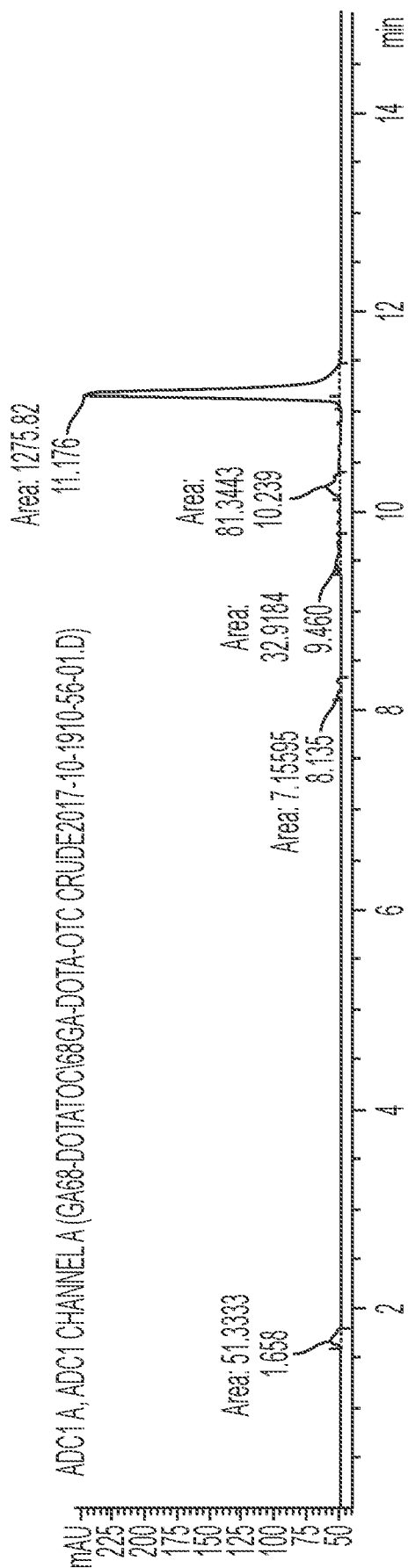


FIG. 1C

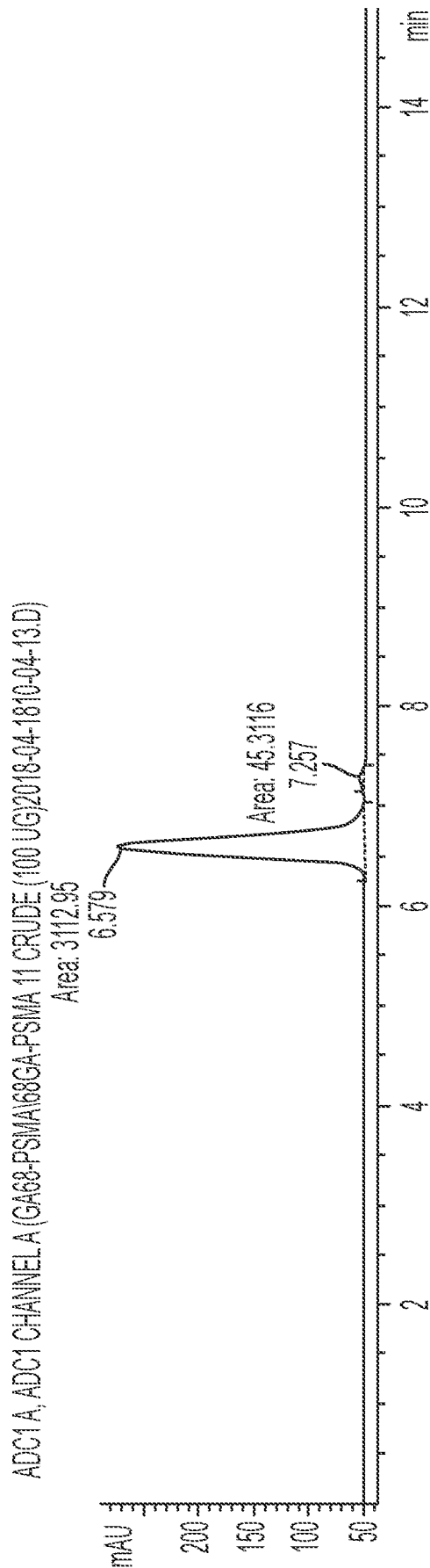


FIG. 2A

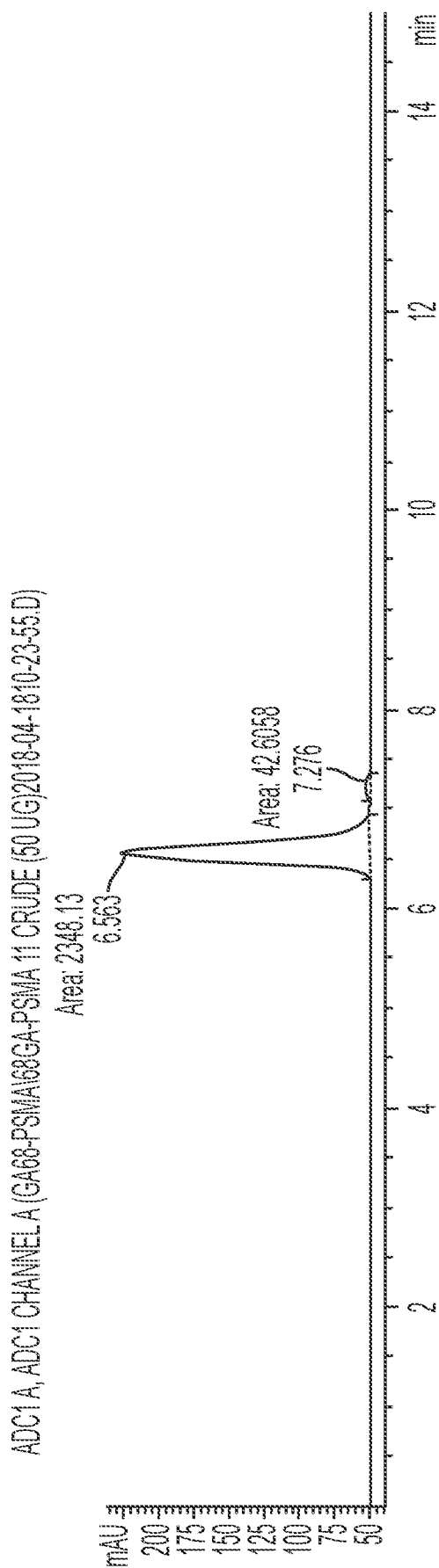


FIG. 2B

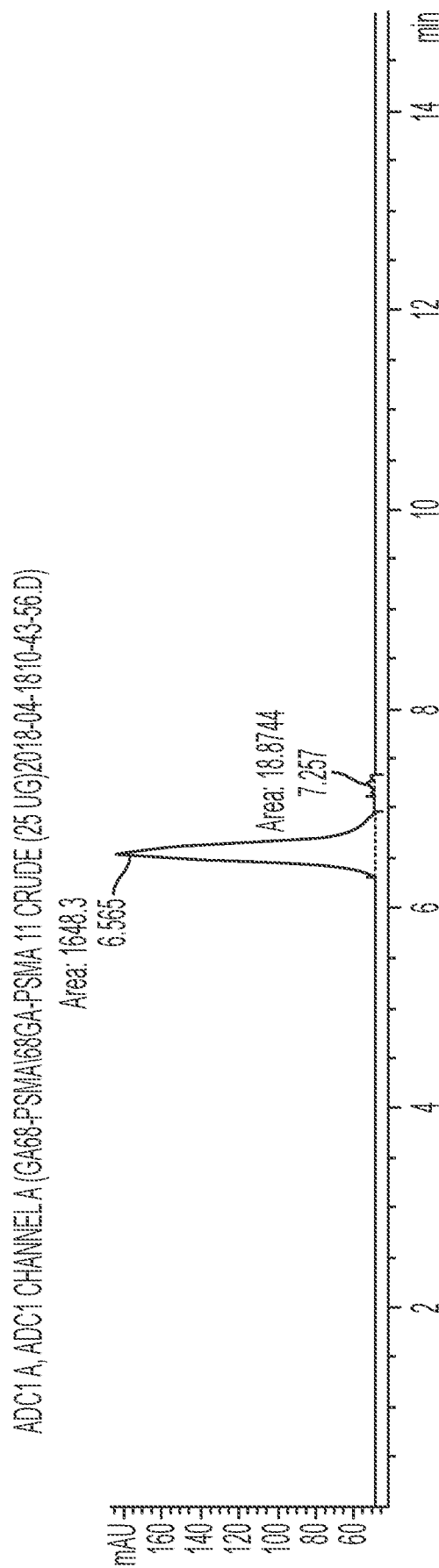


FIG. 2C

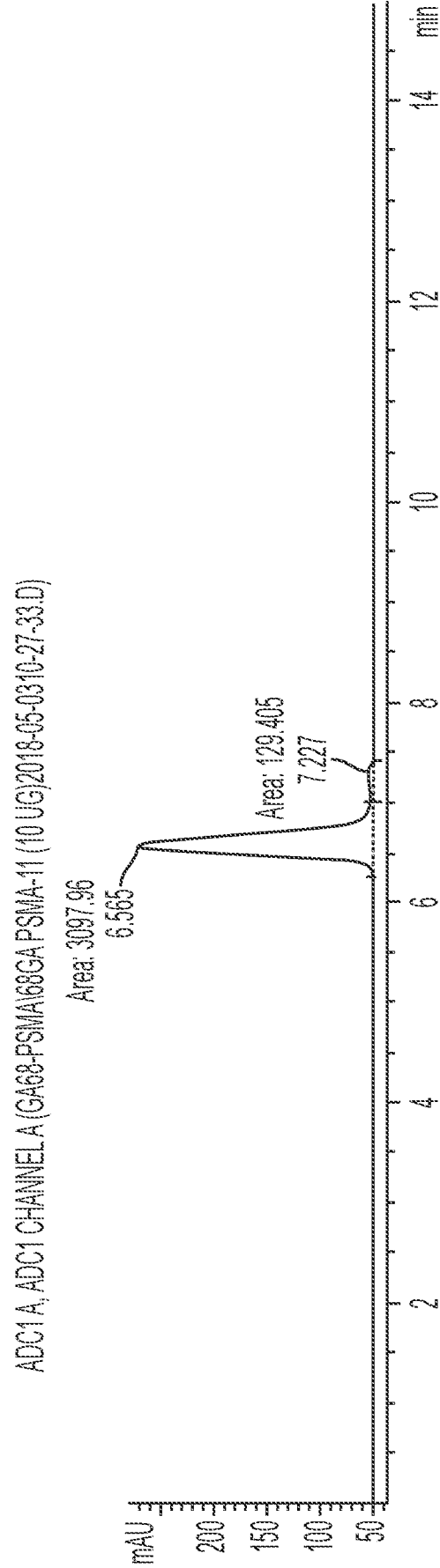


FIG. 3A

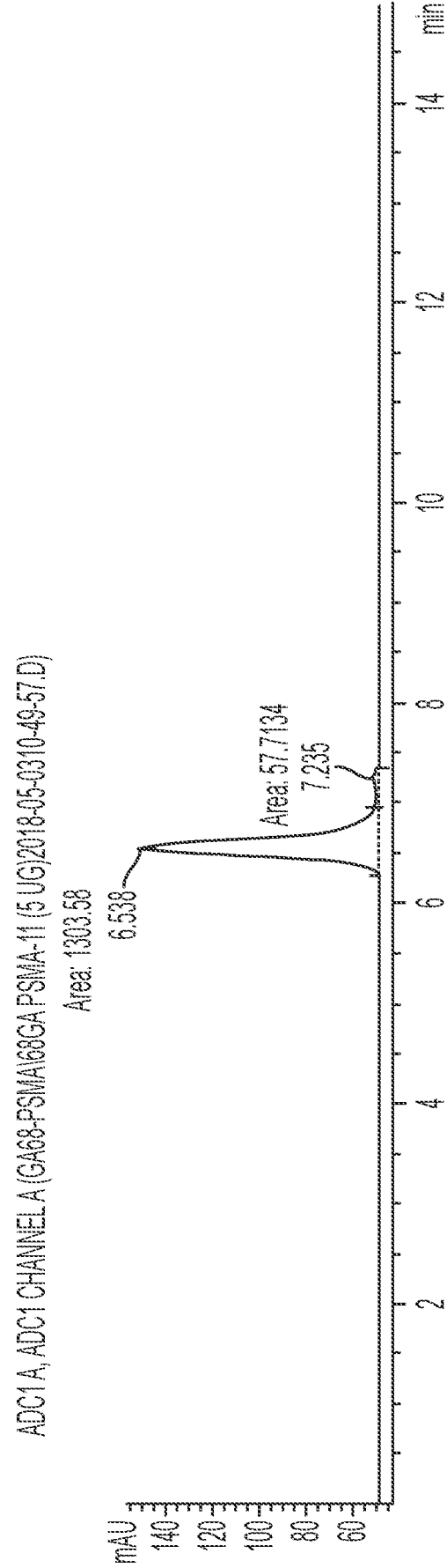


FIG. 3B

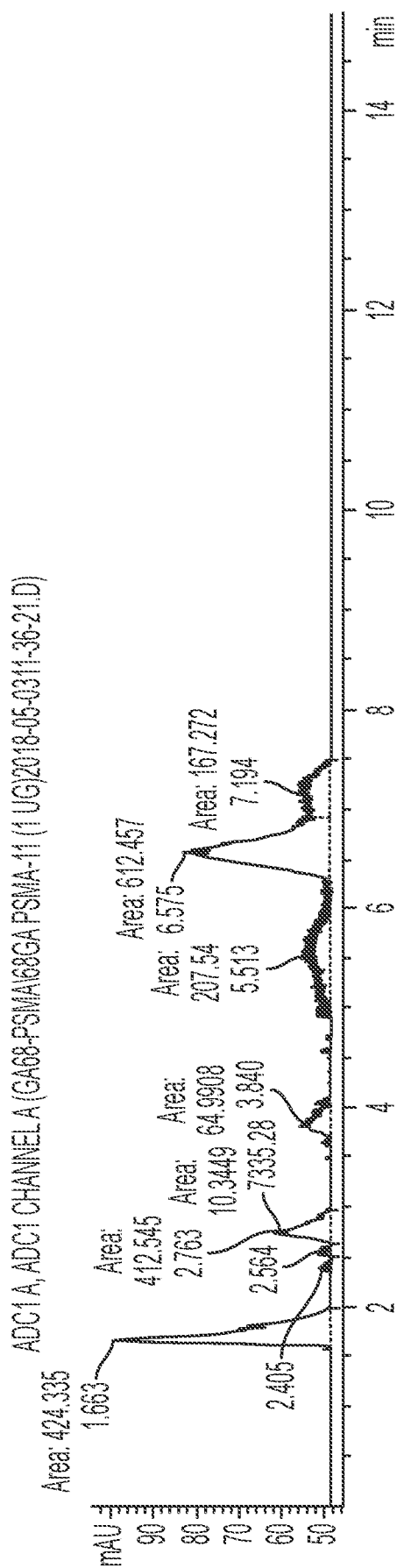


FIG. 3C

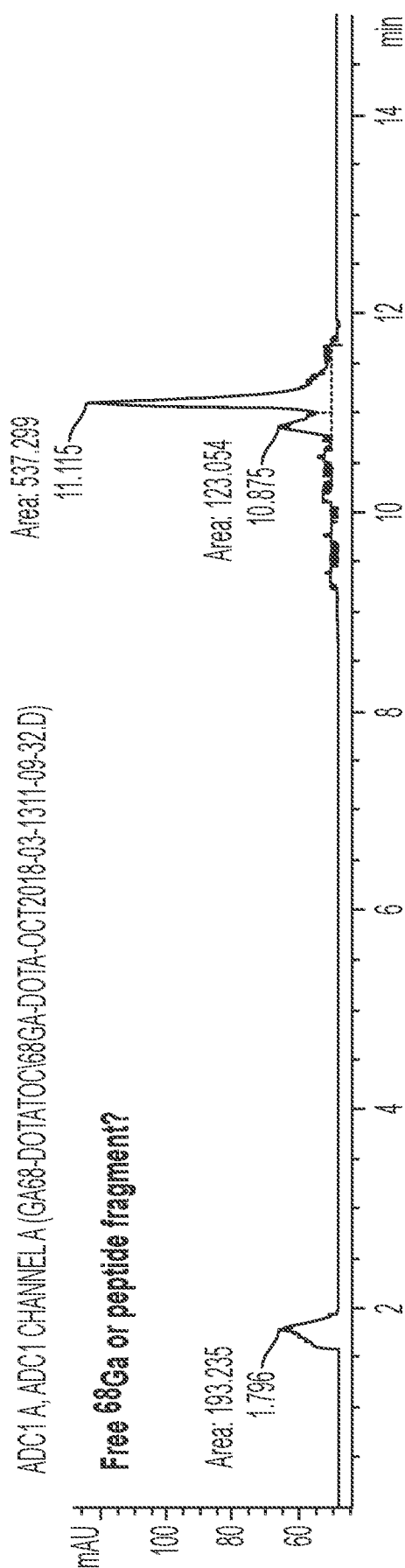


FIG. 4A

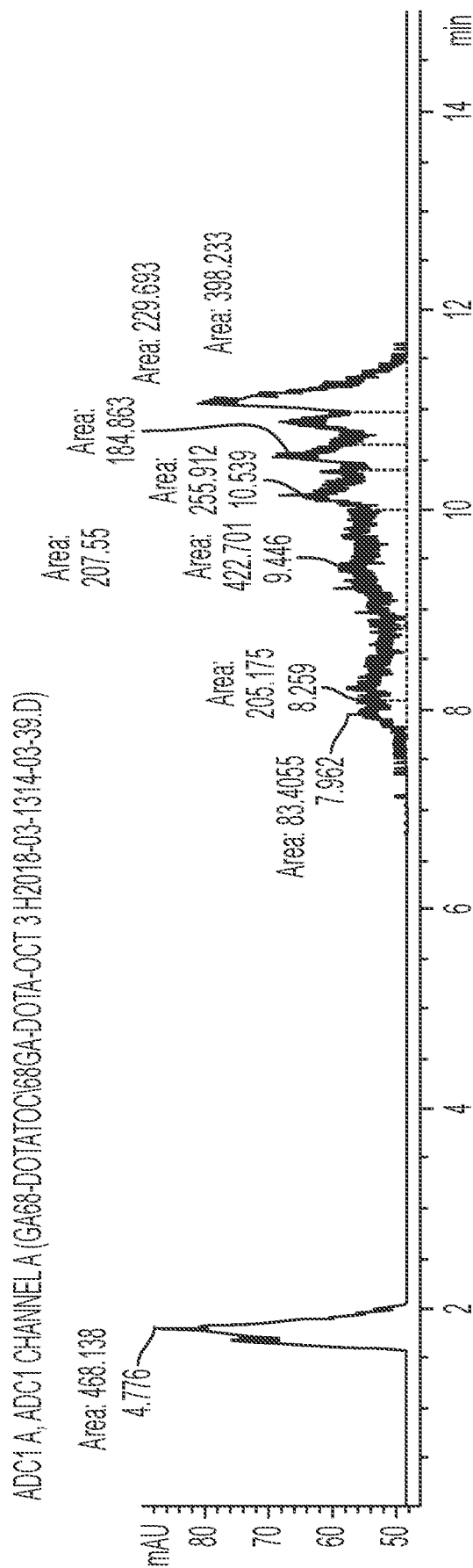


FIG. 4B

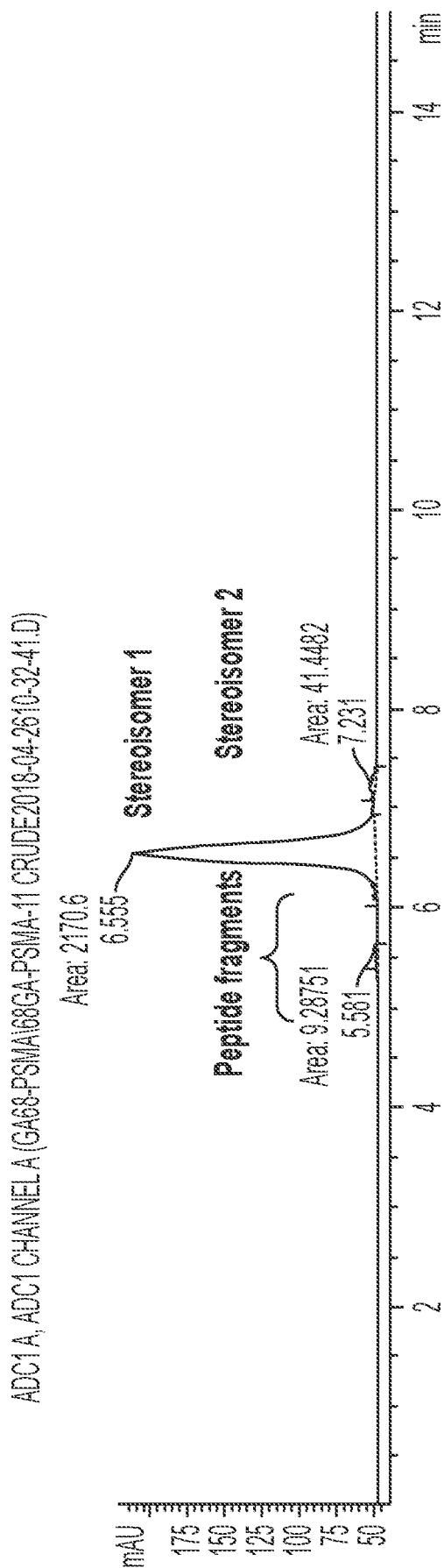


FIG. 5A

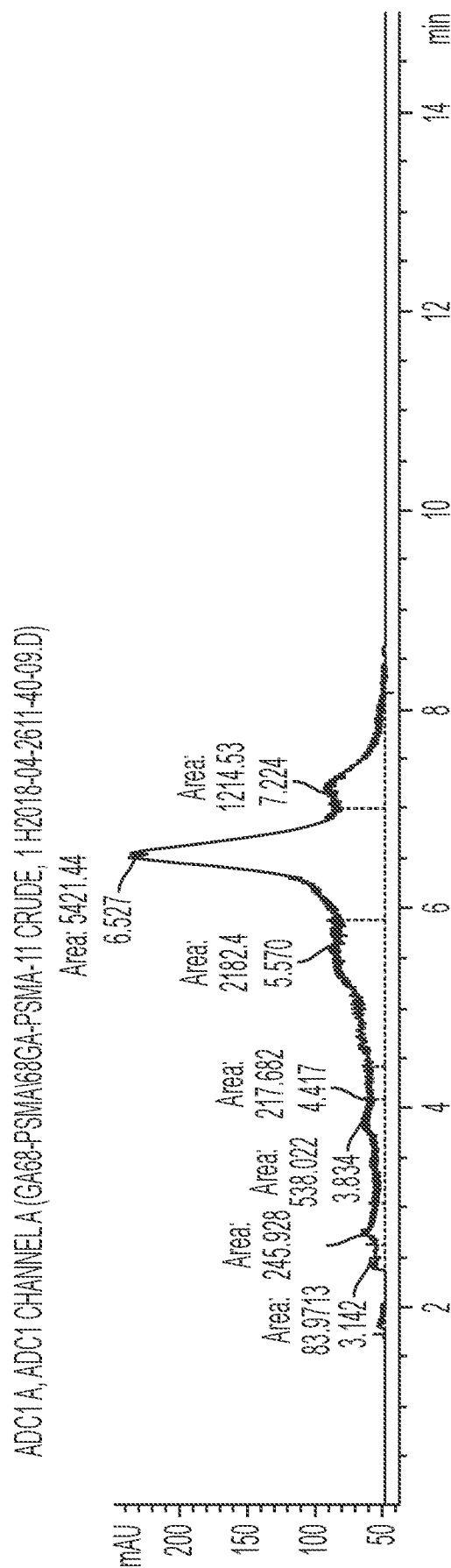


FIG. 5B

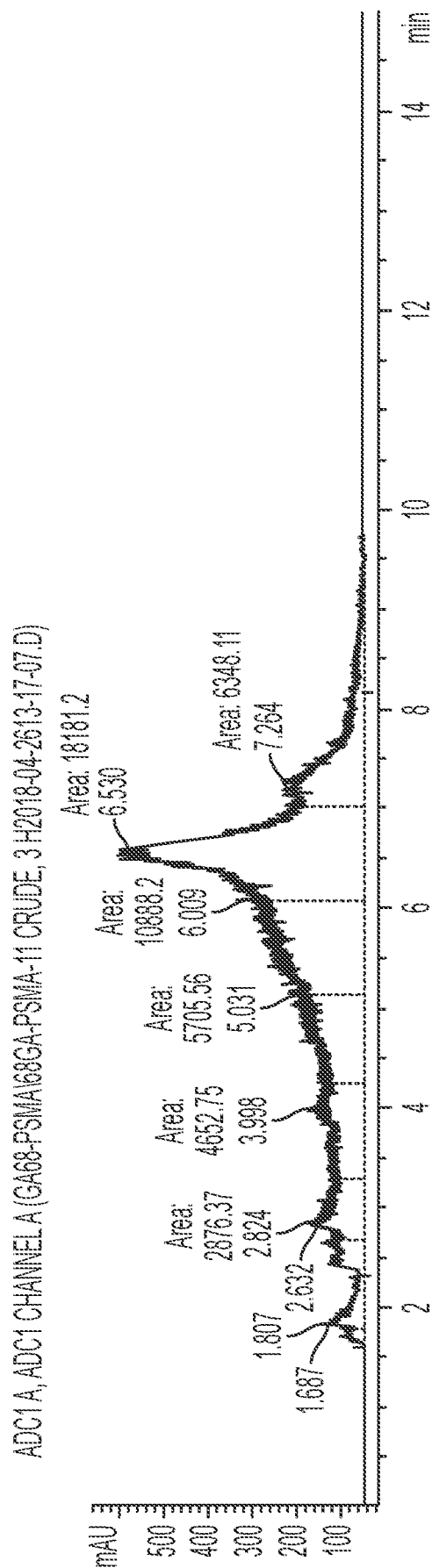


FIG. 5C

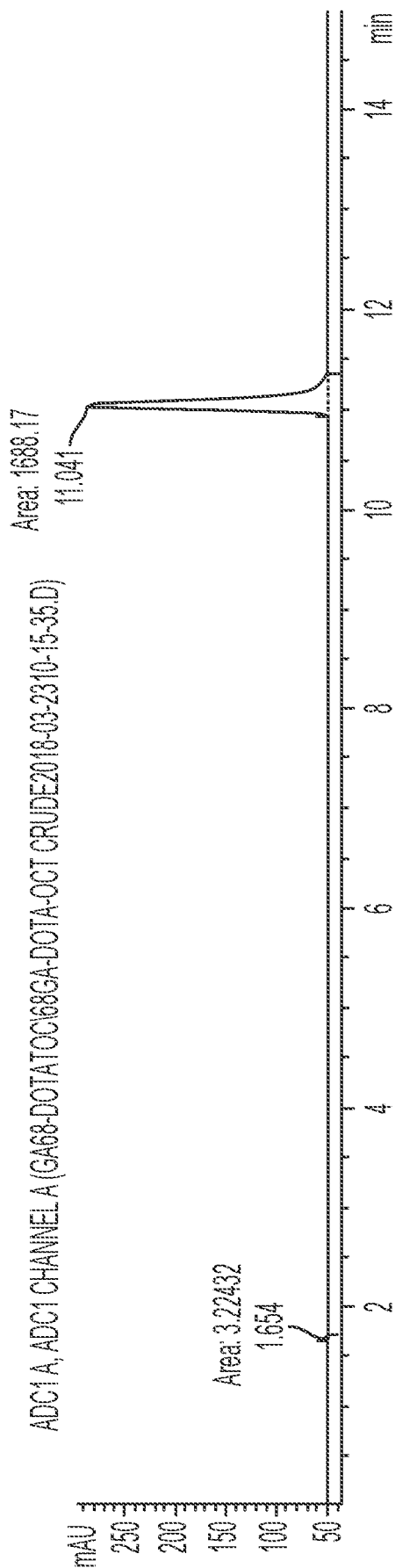


FIG. 6A

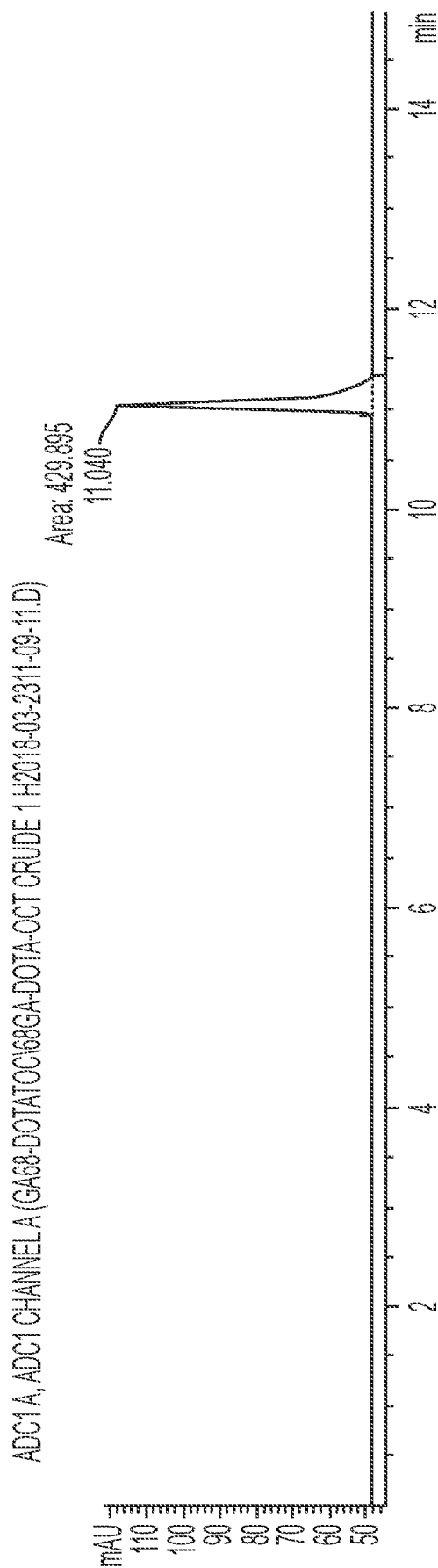


FIG. 6B

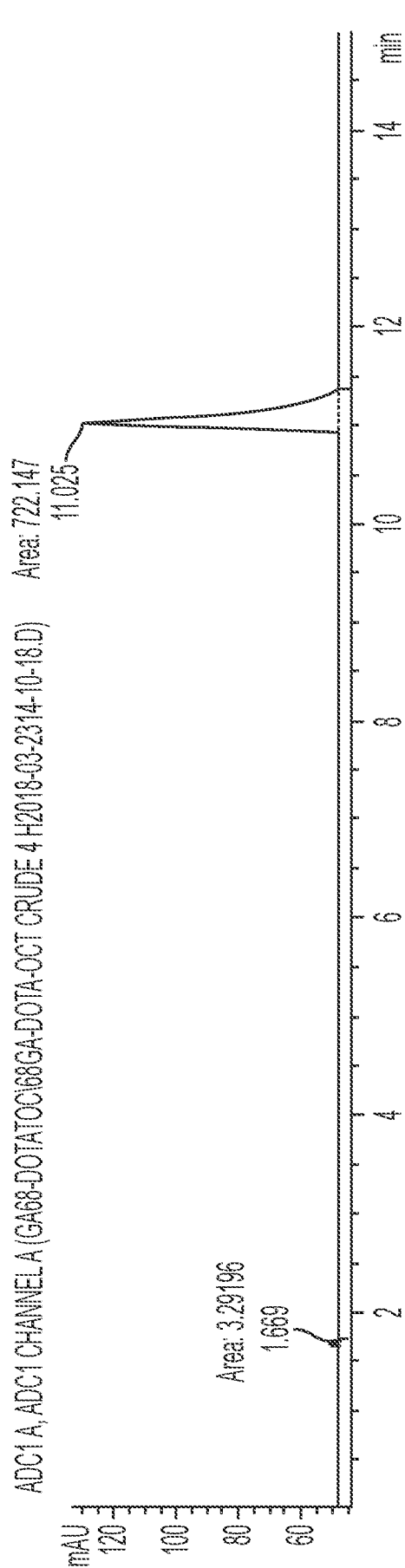


FIG. 6C

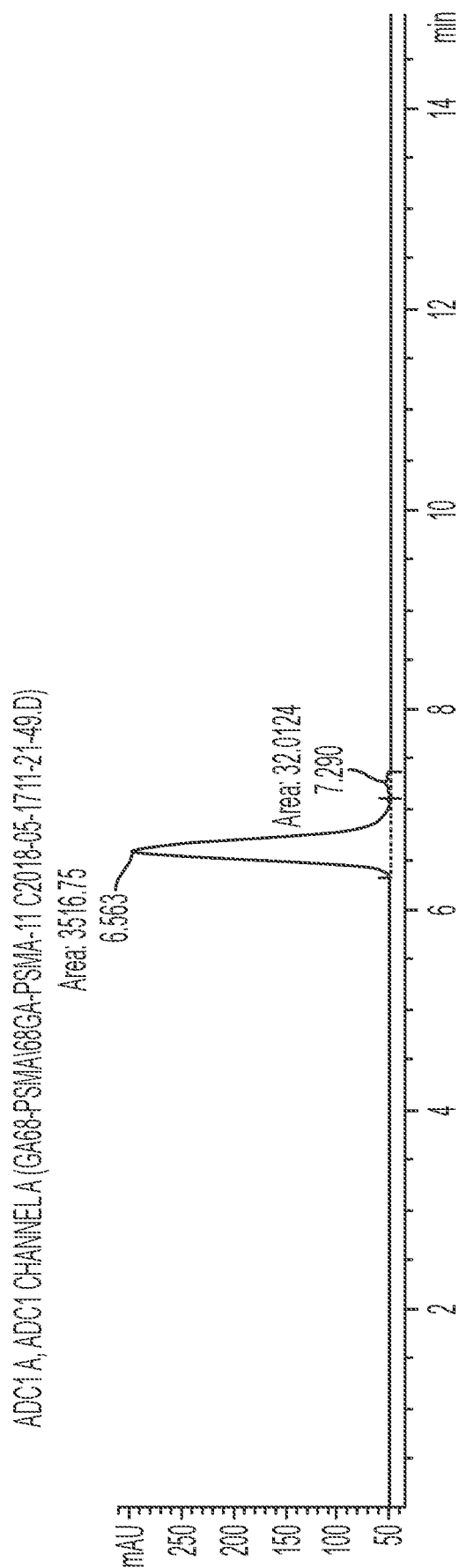


FIG. 7A

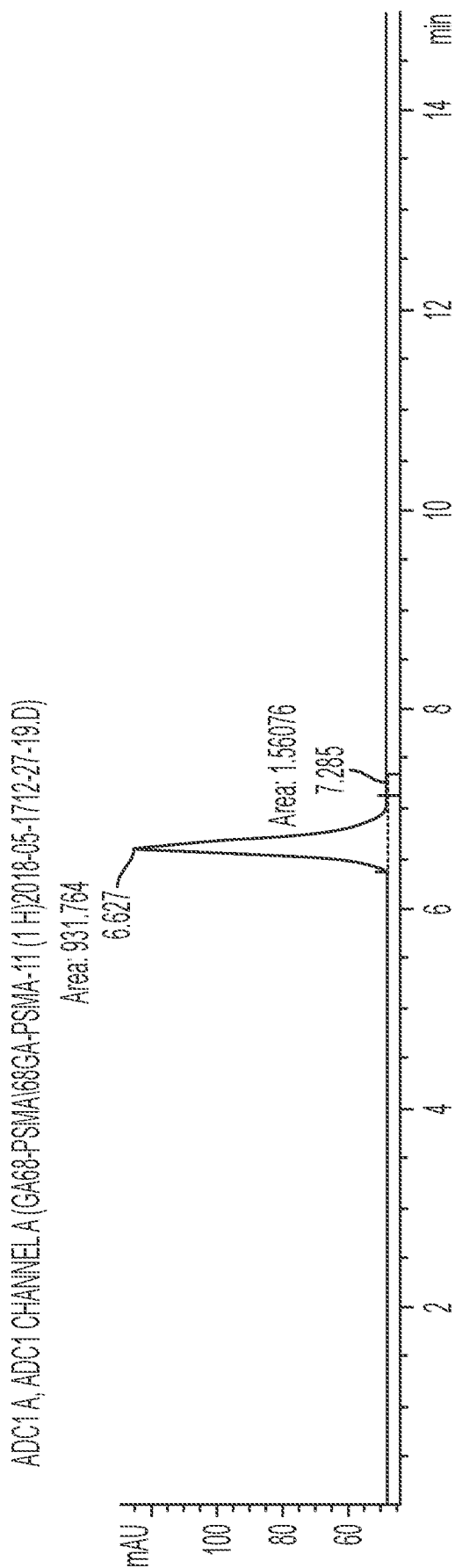


FIG. 7B

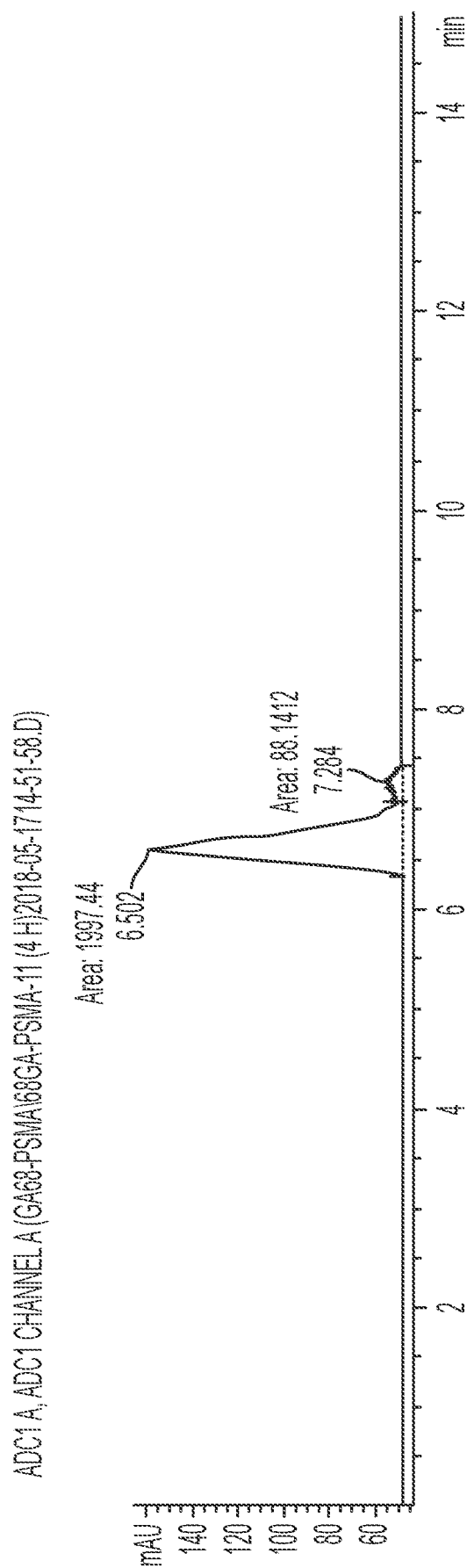


FIG. 7C

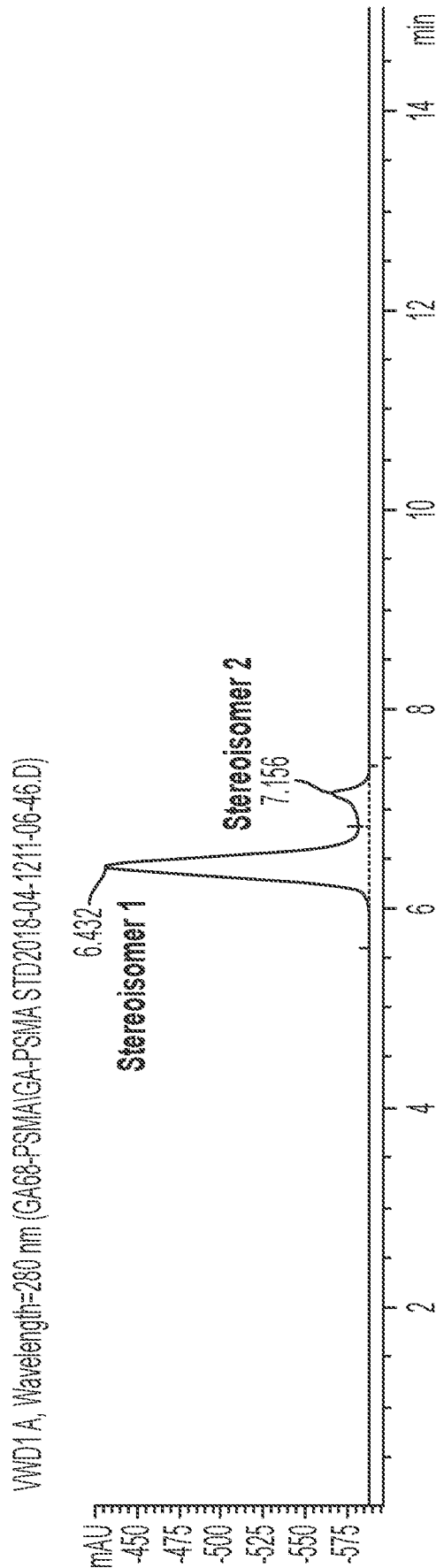


FIG. 8A

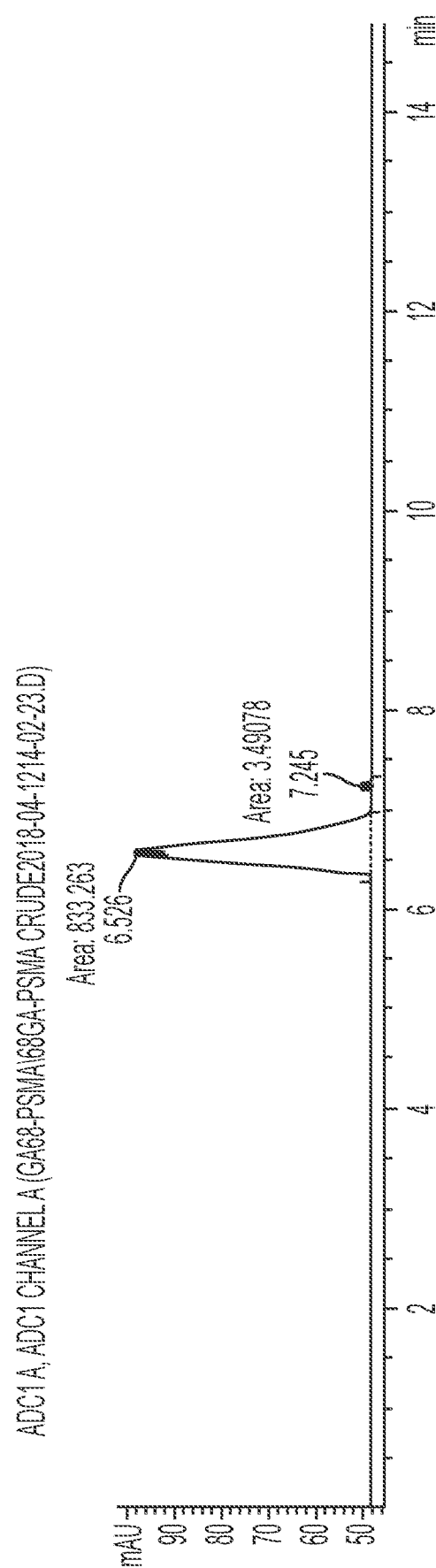


FIG. 8B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/44938

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 51/08; G21G 1/00; G21G 1/10 (2019.01)

CPC - A61K 51/08; C01G 15/00; C01P 2002/87

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2018/0158559 A1 (NCM USA Bronx LLC) 7 June 2018 (07.06.2018) Abstract, para [0005]-[0006], [0011]-[0012], [0015].	1-5, 8-9 ----- 6-7
Y	Pandey, et al. "Cyclotron production of ⁶⁸ Ga via the ⁶⁸ Zn (p, n) ⁶⁸ Ga reaction in aqueous solution." American journal of nuclear medicine and molecular imaging 4.4 (7 June 2014): 303. Abstract, pg 304 col 1 para 1; pg 209 col 1 para 1.	6-7
A	US 2013/0055855 A1 (Van So Le) 7 March 2013 (07.03.2013) Entire Document.	1-9
A	US 2007/0031329 A1 (Velikyan et al.) 8 February 2007 (08.02.2007) Entire Document.	1-9
A	Larenkov, et al. "Preparation of high-purity ⁶⁸ Ga solutions by ion exchange in mixed acetone-hydrochloric acid medium." Radiochemistry 56.1 (1 January 2014): 57-65. Entire Document.	1-9

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

30 September 2019

Date of mailing of the international search report

06 DEC 2019

Name and mailing address of the ISA/US

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P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Lee Young

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/44938

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 10-53, 60-91
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Page

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-9

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/US 19/44938

Lack of Unity Box III:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-9, directed to a method of preparing a ⁶⁸Ga solution.

Group II: Claims 54-59, directed to a system for preparing a ⁶⁸Ga solution.

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I requires the special technical feature of a method of preparing a ⁶⁸Ga solution comprising: obtaining a ⁶⁸Ga solution to be purified comprising ⁶⁸Ga; contacting the ⁶⁸Ga solution with an anion-exchange resin; and eluting the ⁶⁸Ga from the anion-exchange resin to obtain the purified, carrier-free ⁶⁸Ga solution, not required by group II.

Group II requires the special technical feature of a system for preparing a ⁶⁸Ga solution comprising a solid target comprising ⁶⁸Zn; a cyclotron, wherein the solid target is irradiated using the cyclotron, not required by group I.

Common technical features:

Groups I-II share the technical feature of a method or system of preparing a purified, carrier-free ⁶⁸Ga solution comprising: contacting a ⁶⁸Ga solution with an anion-exchange resin.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by US 2018/0158559 A1 to NCM USA Bronx LLC (hereinafter NCM). NCM teaches a method or system of preparing a purified, carrier-free ⁶⁸Ga solution (Abstract, In a system and a method for making carrier-free radioactive isotopic Gallium-68... Gallium-68 is then further purified to remove the impurities resulting in a Gallium-68 composition with high purity; and para [0012], Methods of purifying the carrier free radioactive isotope Ga-68 made according to any one of the above methods and further including purifying the produced Ga-68... Preferably, the Ga-68 is recovered from the ion exchange column using an elution solution and, more preferably, the elution solution is about 0.05 to about 3.0 M hydrochloric acid or equivalents thereof; and para [0015], The carrier molecule is selected from the group consisting of... PSMA... NOTA... DOTA... DTPA; See Instant Specification, pg 5 ln 18-22, In other aspects, the carrier molecule is... PSMA... NOTA... DOTA... DTPA; and pg 18 ln 6-30, ⁶⁸Ga solution comprising ⁶⁸Ga to be purified is contacted with an anion-exchange resin... treated with an acidic solution prior to contacting the resin... ⁶⁸Ga is eluted from the anion-exchange resin) comprising: contacting a ⁶⁸Ga solution with an anion-exchange resin (para [0012], Example embodiments of the present invention also provide methods of purifying the carrier free radioactive isotope Ga-68 made according to any one of the above methods and further including purifying the produced Ga-68 by dissolving the irradiated solid target in a dissolving acid, isolating Ga-68 from the dissolved solid target, washing with at least one washing solution, and recovering purified Ga-68... the Ga-68 is isolated using an ion exchange column and more preferably, the ion exchange column contains an anion exchange resin. Preferably, the ion exchange column containing isolated Ga-68 is washed with at least one washing solution more than once... Preferably, the Ga-68 is recovered from the ion exchange column using an elution solution).

As the technical features were known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I-II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Item 4 (contd.): Claims 10-53 and 60-91 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).