Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AdvanCell Pty Ltd.
Petitioner

v.

Sciencons AS
Patent Owner

Post Grant Review No.: PGR2025-00029

DECLARATION OF SAED MIRZADEH REGARDING PETITION FOR POST GRANT REVIEW OF U.S. PATENT NO. 12,125,603

I hereby declare under penalty of perjury under the laws of the United States of America that the following is true and correct, and that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I understand that willful false statements are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code.

3/9/2025 | 14:32 PDT
Date

DocuSigned by:
Saed Mirzadeh
66F538B3EA8E4BA...
Saed Mirzadeh

1616931162

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

TABLE OF CONTENTS

Page

I. BACKGROUND AND QUALIFICATION 2
A. Materials Considered 2
II. LEGAL STANDARDS 2
A. Legal Standards for Anticipation 2
B. Legal Standards for Obviousness 3
III. THE 603 PATENT 8
A. Overview of the 603 patent 8
B. Overview of the 603 patent's File History 8
C. Person of Ordinary Skill in the Art 10
D. Claim Construction 10
1. "disposed on the rod" (claim 1) 10
2. "wherein exposing the interior surface of the container to the precursor isotope source exposing the interior surface of the container to the precursor isotope source without having the precursor isotope source touch the interior surface." (claim 7) 11
3. "allowing sufficient time for the precursor isotope source to decay comprises allowing 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours" (claim 10) 12
4. "the precursor isotope source is configured to decay and emanate the one or more progeny isotopes into the container for 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours" (claim 20) 12
IV. GROUND 1: CLAIMS 1-8, 11-17, AND 19 ARE ANTICIPATED BY HASSFJELL-HOFF 13
A. Overview of Hassfjell-Hoff 13
B. Claim 1 19
1. [1pre] A method of generating radioisotopes, the method comprising: 20

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

2. [1a] exposing an interior surface of a container to a precursor isotope source by sliding a rod from a closed position in which the precursor isotope source is sealed off from the interior surface of the container to an open position in which the precursor isotope source is exposed to the interior surface of the container 21

3. [1b] wherein the precursor isotope source is disposed on the rod 24

4. [1c] allowing sufficient time for the precursor isotope source to decay into one or more progeny isotopes and to emanate the one or more progeny isotopes into the container; and 25

5. [1d] isolating the precursor isotope source from the container by sliding the rod from the open position to the closed position 26

C. Claim 2 "The method of claim 1, wherein exposing the interior surface to the precursor isotope source comprises exposing the interior surface to a thorium 228 isotope (228Th) and/or a radium 224 isotope (224Ra), the method further comprising allowing the 228Th to decay into at least one of a radon 220 isotope (220Rn) and a lead 212 isotope (212Pb)." 26

D. Claim 3 "The method of claim 2, the method further comprising allowing the 212Pb to deposit on the interior surface of the container." 27

E. Claim 4 "The method of claim 1, wherein isolating the precursor isotope source from the container further comprises withdrawing the precursor isotope source into a chamber having a gas tight seal." 28

F. Claim 5 "The method of claim 4, wherein withdrawing the precursor isotope source into a gas tight seal comprises sealing the rod within a tube using an O-ring to form the gas tight seal between the rod and the tube." 29

G. Claim 6 "The method of claim 1, the method further comprising turning the container before exposing the interior surface to the precursor isotope." 32

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

H. Claim 7 "The method of claim 1, wherein exposing the interior surface of the container to the precursor isotope source exposing the interior surface of the container to the precursor isotope source without having the precursor isotope source touch the interior surface." 34

I. Claim 8 "The method of claim 1, wherein allowing sufficient time for the at least one progeny isotopes to emanate into the container comprises allowing the at least one progeny isotopes to emanate into the container from the precursor isotope source through a gas permeable barrier." 37

J. Claim 11 "The method of claim 1, the method further comprising changing an orientation of the container before exposing the interior surface to the precursor isotope."....39

K. Claim 12 39

1. [12pre] A system for generating radioisotopes, the system comprising.....40

2. [12a] a precursor isotope source disposed on a rod, the rod configured to slide between an open position in which the precursor isotope is exposed to an interior surface of a container to allow the precursor isotope source to decay into one or more progeny isotopes emanated into the container, and 40

3. [12b] a closed position in which the precursor isotope source is sealed off from the container to isolate the precursor isotope source from the interior surface. 41

L. Claim 13 "The system of claim 12, wherein the precursor isotope source comprises a thorium 228 isotope (228Th) and/or a radium 224 isotope (224Ra), the one or more progeny isotopes comprising at least one of a radon 220 isotope (220Rn) and a lead 212 isotope (212Pb)." 41

M. Claim 14 "The system of claim 12, wherein, in the closed position, the rod forms a gas tight seal with a tube in which the rod slides to isolate the precursor isotope source from the interior surface." 42

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

N. Claim 15 "The system of claim 14, wherein the rod includes at least one O-ring to form the gas tight seal with the tube in the closed position." 43

O. Claim 16 "The system of claim 12, wherein the rod holds the precursor isotope source without having the precursor isotope source touch the interior surface." 45

P. Claim 17 "The system of claim 12, wherein the precursor isotope source is encapsulated in a gas permeable barrier." 47

Q. Claim 19 "The system of claim 13, further comprising the container, wherein the interior surface of the container is configured to allow the 212Pb to deposit on the interior surface." 48

V. GROUND 2: CLAIMS 5-7, 10-11, 15-16, AND 20 ARE OBVIOUS OVER HASSFJELL-HOFF 48

A. Overview of Hassfjell-Hoff 48

B. Claim 5 "The method of claim 4, wherein withdrawing the precursor isotope source into a gas tight seal comprises sealing the rod within a tube using an O-ring to form the gas tight seal between the rod and the tube." 48

C. Claim 6 "The method of claim 1, the method further comprising turning the container before exposing the interior surface to the precursor isotope." 50

D. Claim 7 "The method of claim 1, wherein exposing the interior surface of the container to the precursor isotope source [sic] exposing the interior surface of the container to the precursor isotope source without having the precursor isotope source touch the interior surface." 51

E. Claim 10 "The method of claim 1, wherein allowing sufficient time for the precursor isotope source to decay comprises allowing 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours." 52

F. Claim 11 "The method of claim 1, the method further comprising changing an orientation of the container before exposing the interior surface to the precursor isotope." 54

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

G. Claim 15 "The system of claim 14, wherein the rod includes at least one O-ring to form the gas tight seal with the tube in the closed position." 56

H. Claim 16 "The system of claim 12, wherein the rod holds the precursor isotope source without having the precursor isotope source touch the interior surface." 58

I. Claim 20 "The system of claim 12, wherein the precursor isotope source is configured to decay and emanate the one or more progeny isotopes into the container for 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours." 59

VI. GROUND 3: CLAIMS 9-10, 18, 20 ARE OBVIOUS OVER HASSFJELL-HOFF AND O'HARA 60

A. Overview of Hassfjell-Hoff 60

B. Overview of O'Hara 60

C. Claim 9 "The method of claim 1, wherein allowing sufficient time for the at least one progeny isotopes to emanate into the container from the precursor isotope source comprises allowing sufficient time for the at least one progeny isotopes to emanate into the container from the precursor isotope source disposed in a sponge, a wool, a strip, or a sphere comprising at least one selected from the group consisting of: quartz, glass, mineral, paper, plastic, metal, ceramic, natural fibers, and synthetic fibers." 61

1. Hassfjell Discussion 62

2. O'Hara Discussion 62

3. Motivation to Combine 63

D. Claim 10 "The method of claim 1, wherein allowing sufficient time for the precursor isotope source to decay comprises allowing 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours." 64

E. Claim 18 "The system of claim 12, wherein the precursor isotope source is disposed on a sponge, a wool, a strip, or a sphere comprising at least one material selected from the group consisting of: quartz, glass, mineral, paper, plastic, metal, ceramic, natural fibers, and synthetic fibers." 66

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

F. Claim 20 "The system of claim 12, wherein the precursor isotope source is configured to decay and emanate the one or more progeny isotopes into the container for 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours." 67

VII. GROUND 4: CLAIMS 1-3, 7-10, 12, 20 ARE UNPATENTABLE UNDER 35 U.S.C. §112 67

A. Claim 1 is non-enabled and lacks written description 67

B. Claim 2 is indefinite and non-enabled 69

C. Claim 3 is indefinite and non-enabled 70

D. The language of Claim 7 is non-sensical, therefore indefinite 70

E. Claims 8 and 9 are indefinite for lack of antecedent basis.....71

F. Claim 10 is indefinite and lack written description 71

G. Claim 12 is non-enabled and lacks written description 72

H. Claim 20 is indefinite, lacks written description, and is non-enabled.....72

VIII. SECONDARY CONSIDERATIONS 72

IX. AVAILABILITY FOR CROSS-EXAMINATION 73

X. RIGHT TO SUPPLEMENT 73

XI. CONCLUSION.....73

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

INDEX OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent Number 12,125,603.
1002	RESERVED
1003	Hassfjell, Sindre P. and Hoff, Per, "A Generator for Production of ^{212}Pb and ^{212}Bi", Appl. Radiat. Isot., vol. 45, no. 10, pp 6-25 (1994) ("**Hassfjell-Hoff**").
1004	WorldCat Index for **Hassfjell-Hoff**.
1005	International Publication Number WO 01/60417.
1006	File History of U.S. Patent No. 12,125,603.
1007	US Patent Application Publication No. 2018/0047474 A1("**O'Hara**").
1008	Hassan, Ahmed and Alnaser, Ibrahim Abdullah, "A Review of Different Manufacturing Methods of Metallic Foams" ACS Omega 2024 9 (6), 6280-6295 DOI: 10.1021/acsomega.3c08613 ("**Hassan**").
1009	Lefebvre, Louis-Philippe, Banhart, John, and Dunand, David C., "Porous Metals and Metallic Foams: Current Status and Recent Developments," Advanced Engineering Materials, 10, September 9, pp. 775-787, 2008 https://doi.org/10.1002/adem.200800241, ("**Lefebvre**").
1010	U.S. Patent Number 3,087,807.
1011	"Radioisotopes," International Atomic Energy Agency, https://www.iaea.org/topics/nuclear-science/isotopes/radioisotopes (last accessed February 11, 2025).
1012	File History of U.S. Patent Application Serial No. 18/680,605.
1013	File History of U.S. Patent Application Serial No. 18/680,372.
1014	Hassfjell, Sindre, "A ^{212}Pb generator based on a ^{228}Th source", Appl. Radiat. Isot., vol. 55, no. 4, pp 433-439 (2001) ("**Hassfjell-2001**").
1015	U.S. Patent Number 6,592,843.
1016	"O-Ring Handbook," Parker Hannifin Corporation, https://www.hdslippers.com/cgi-bin/pdf/Catalogues/05-O-Ring-Handbook_ODE5705-EN%20Luglio%202015.pdf (last accessed March 7, 2025).

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

CHART OF CLAIMS
[1pre] A method of generating radioisotopes, the method comprising:
[1a] exposing an interior surface of a container to a precursor isotope source by sliding a rod from a closed position in which the precursor isotope source is sealed off from the interior surface of the container to an open position in which the precursor isotope source is exposed to the interior surface of the container, wherein the precursor isotope source is disposed on the rod;
[1b] allowing sufficient time for the precursor isotope source to decay into one or more progeny isotopes and to emanate the one or more progeny isotopes into the container; and
[1c] isolating the precursor isotope source from the container by sliding the rod from the open position to the closed position.
[2] The method of claim 1, wherein exposing the interior surface to the precursor isotope source comprises exposing the interior surface to a thorium 228 isotope (^{228}Th) and/or a radium 224 isotope (^{224}Ra), the method further comprising allowing the ^{228}Th to decay into at least one of a radon 220 isotope (^{220}Rn) and a lead 212 isotope (^{212}Pb).
[3] The method of claim 2, the method further comprising allowing the ^{212}Pb to deposit on the interior surface of the container.
[4] The method of claim 1, wherein isolating the precursor isotope source from the container further comprises withdrawing the precursor isotope source into a chamber having a gas tight seal.
[5] The method of claim 4, wherein withdrawing the precursor isotope source into a gas tight seal comprises sealing the rod within a tube using an O-ring to form the gas tight seal between the rod and the tube.
[6] The method of claim 1, the method further comprising turning the container before exposing the interior surface to the precursor isotope.
[7] The method of claim 1, wherein exposing the interior surface of the container to the precursor isotope source exposing the interior surface of the container to the precursor isotope source without having the precursor isotope source touch the interior surface.
[8] The method of claim 1, wherein allowing sufficient time for the at least one progeny isotopes to emanate into the container comprises allowing the at least one progeny isotopes to emanate into the container from the precursor isotope source through a gas permeable barrier.
[9] The method of claim 1, wherein allowing sufficient time for the at least one progeny isotopes to emanate into the container from the precursor isotope source comprises allowing sufficient time for the at least one progeny isotopes to emanate into the container from the precursor isotope source disposed in a

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

CHART OF CLAIMS
sponge, a wool, a strip, or a sphere comprising at least one selected from the group consisting of: quartz, glass, mineral, paper, plastic, metal, ceramic, natural fibers, and synthetic fibers.
[10] The method of claim 1, wherein allowing sufficient time for the precursor isotope source to decay comprises allowing 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours.
[11] The method of claim 1, the method further comprising changing an orientation of the container before exposing the interior surface to the precursor isotope.
[12] A system for generating radioisotopes, the system comprising:
[12a] a precursor isotope source disposed on a rod, the rod configured to slide between an open position in which the precursor isotope is exposed to an interior surface of a container to allow the precursor isotope source to decay into one or more progeny isotopes emanated into the container, and a closed position in which the precursor isotope source is sealed off from the container to isolate the precursor isotope source from the interior surface.
[13] The system of claim 12, wherein the precursor isotope source comprises a thorium 228 isotope (^{228}Th) and/or a radium 224 isotope (^{224}Ra), the one or more progeny isotopes comprising at least one of a radon 220 isotope (^{220}Rn) and a lead 212 isotope (^{212}Pb).
[14] The system of claim 12, wherein, in the closed position, the rod forms a gas tight seal with a tube in which the rod slides to isolate the precursor isotope source from the interior surface.
[15] The system of claim 14, wherein the rod includes at least one O-ring to form the gas tight seal with the tube in the closed position.
[16] The system of claim 12, wherein the rod holds the precursor isotope source without having the precursor isotope source touch the interior surface.
[17] The system of claim 12, wherein the precursor isotope source is encapsulated in a gas permeable barrier.
[18] The system of claim 12, wherein the precursor isotope source is disposed on a sponge, a wool, a strip, or a sphere comprising at least one material selected from the list consisting of: quartz, glass, mineral, paper, plastic, metal, ceramic, natural fibers, and synthetic fibers.
[19] The system of claim 13, further comprising the container, wherein the interior surface of the container is configured to allow the ^{212}Pb to deposit on the interior surface.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

CHART OF CLAIMS
[20] The system of claim 12, wherein the precursor isotope source is configured to decay and emanate the one or more progeny isotopes into the container for 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

I, Saed Mirzadeh, declare as follows:

1. My name is Saed Mirzadeh. I have been asked by Petitioner AdvanCell Pty Ltd. ("Petitioner") to provide my expert opinions in support of the above-identified petition for *post grant* review of claims 1-20 ("Challenged Claims") of U.S. Patent No. 12,125,603 ("603 patent," EX1001). I have been informed that the 603 patent is owned by Sciencons AS ("Sciencons AS").

2. I currently hold the opinions set forth in this Declaration.

3. In summary, it is my opinion that the references cited below render unpatentable the Challenged Claims. My detailed opinions on the claims are set forth below. In this Declaration, I offer opinions on the following grounds:

Ground	Claims	Stat. Basis	Prior Art
1	1-8, 11-17, 19	102	Hassfjell-Hoff
2	5-7, 10-11, 15-16, 20	103	Hassfjell-Hoff
3	9-10, 18, 20	103	Hassfjell-Hoff and O'Hara
4	1-3, 7-10, 12, 20	112	

4. I am being compensated for my time at the rate of $300 per hour. This compensation is not contingent upon my performance, the outcome of this matter, or any issues involved in or related to this matter.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

I. BACKGROUND AND QUALIFICATION

5. All of my opinions stated herein are based on my own personal knowledge, professional judgment, and analysis of the materials and information I considered in preparing this Declaration. In forming my opinions, I have relied on my knowledge and experience in designing, developing, researching, and teaching the technology referenced in this Declaration.

6. I am over 18 years of age and, if I am called upon to do so, I would be competent to testify as to the matters set forth herein. I understand that a copy of my current curriculum vitae, which details my education and professional and academic experience, is being submitted as Appendix 1.

A. Materials Considered

7. In preparing this Declaration, I have reviewed and/or considered at least the documents cited in the Index of Exhibits, and the documents referenced in this Declaration. I have also reviewed the prosecution history of the 603 patent.

II. LEGAL STANDARDS

A. Legal Standards for Anticipation

8. I have been informed that documents and materials that qualify as prior art can be used to invalidate a patent claim via anticipation or obviousness.

9. I have been informed that, once the claims of a patent have been properly construed, the second step in determining anticipation of a patent claim

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

requires a comparison of the properly construed claim language to the prior art on a limitation-by-limitation basis.

10. I have been informed that a prior art reference "anticipates" an asserted claim, and thus renders the claim invalid, if all elements of the claim are disclosed in that prior art reference, either explicitly or inherently (*i.e.*, necessarily present), arranged as claimed and in an enabling manner.

11. I have been informed that anticipation in a post grant review must be shown by a preponderance of the evidence.

B. Legal Standards for Obviousness

12. I have been informed that even if a patent claim is not anticipated, it is still invalid if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the pertinent art.

13. I have been informed that a person of ordinary skill in the art provides a reference point from which the prior art and claimed invention should be viewed. This reference point prevents one from using his or her own insight or hindsight in deciding whether a claim is obvious.

14. I also have been informed that an obviousness determination includes the consideration of various factors such as (1) the scope and content of the prior art, (2) the differences between the prior art and the asserted claims, (3) the level of

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

ordinary skill in the pertinent art, and (4) the existence of secondary considerations such as commercial success, long-felt but unresolved needs, failure of others, etc.

15. I have been informed that an obviousness evaluation can be based on a combination of multiple prior art references. I have been informed that the prior art references themselves may provide a suggestion, motivation, or reason to combine, but other times the nexus linking two or more prior art references is simple common sense. I further have been informed that obviousness analysis recognizes that market demand, rather than scientific literature, often drives innovation, and that a motivation to combine references may be supplied by the direction of the marketplace.

16. I have been informed that if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

17. I have been informed that practical and common-sense considerations should guide a proper obviousness analysis, because familiar items may have obvious uses beyond their primary purposes. I have been informed that a person of ordinary skill in the art looking to overcome a problem will often be able to fit together the teachings of multiple publications. I have been informed that an

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

obviousness analysis therefore takes into account the inferences and creative steps that a person of ordinary skill in the art would employ under the circumstances.

18. I have been informed that a particular combination may be proven obvious merely by showing that it was obvious to try the combination. For example, when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp because the result is likely the product not of innovation but of ordinary skill and common sense.

19. I have been informed that the combination of familiar elements according to known methods is likely to be obvious when it does no more than have predictable results. I have been informed that when a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. I have also been informed that if a person of ordinary skill can implement a predictable variation, the patent claim is likely obvious.

20. I have been informed that a proper obviousness analysis focuses on what was known or obvious to a person of ordinary skill in the art, not just the patentee. Accordingly, I have been informed that any need or problem known in

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

21. I have been informed that a proposed obviousness combination does not need to be the preferred, or most desirable, combination available, in order to render a claim obvious. I have been informed that, instead, there must be something that suggests the desirability of the proposed combination, not necessarily something that suggests that the proposed combination is the most desirable combination available.

22. Similarly, I have been informed that for purposes of obviousness, when a motivating benefit comes at the expense of another benefit, that does not nullify the proposed obviousness combination or modification. Likewise, I have been informed that a proposed obviousness combination does not fail merely because it may be inferior to other systems used for the same use.

23. I have been informed that a determination of obviousness based on teachings from multiple references does not require an actual, physical substitution of elements between the multiple references. I have been informed that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference. Instead, I have been informed that the test is whether a claim is rendered obvious by the teachings of the prior art as a whole.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

24. I have been informed that a claim can be obvious in light of a single reference, without the need to combine references, if the elements of the claim that are not found explicitly or inherently in the reference can be supplied by the common sense of one of skill in the art.

25. I have been informed that secondary indicia of non-obviousness may include: (1) a long felt but unmet need in the prior art that was satisfied by the invention of the patent; (2) commercial success of processes covered by the patent; (3) unexpected results achieved by the invention; (4) praise of the invention by others skilled in the art; (5) taking of licenses under the patent by others; (6) deliberate copying of the invention; (7) failure of others to find a solution to the long felt need; and (8) skepticism by experts.

26. I have been informed that there must be a relationship between any such secondary considerations and the invention. I have been informed that contemporaneous and independent invention by others is a secondary consideration supporting an obviousness determination.

27. In sum, my understanding is that prior art teachings are properly combined where a person of ordinary skill in the art having the understanding and knowledge reflected in the prior art and motivated by the general problem facing the inventor, would have been led to make the combination of elements recited in the claims. Under this analysis, the prior art references themselves, or any need or

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

problem known in the field of endeavor at the time of the invention, can provide a reason for combining the elements of multiple prior art references in the claimed manner.

28. I have been informed that obviousness in a post grant review must be shown by a preponderance of the evidence.

III. THE 603 PATENT

A. Overview of the 603 patent

29. The 603 patent describes a method and a system for producing highly purified ^{212}Pb, a radioactive isotope utilized in targeted alpha therapy for cancer treatment. EX1001, cls. 1, 12, 9:64-67. The process involves isolating and purifying ^{212}Pb from mixtures containing other isotopes through a specific decay chain that begins with ^{228}Th. EX1001, Fig. 1. The resulting ^{212}Pb is intended for use in producing radiopharmaceuticals, enhancing the effectiveness of cancer therapies. EX1001, 17:18-21.

30. I have been informed that, based on the face of the patent, the priority date for this patent is December 5, 2019.

B. Overview of the 603 patent's File History

31. The 603 patent was filed on June 2, 2022 as a national stage application. EX1001, cover. EX1006, 37-44, 51-55. The national stage entry was filed with a preliminary amendment that amended claim 1, canceled claims 2-38, and presented new claims 39-75. EX1006, 8-12. The 603 patent was first published

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

on January 19, 2023 as US Patent Application Publication No. 2023/0014219. EX1001, Cover. *See* EX1006, 220. On May 12, 2023, the Applicant filed a preliminary amendment that canceled claim 1. The examiner never issued a rejection based on the prior art that I describe in this Declaration, and sent a Notice of Allowability on August 6, 2024. EX1006, 259-260. A Corrected Notice of Allowability was sent by the USPTO on August 29, 2024. EX1006, 278-279. As stated in both the Notice of Allowability and the Corrected Notice of Allowability, the Examiner's reasons for allowance were:

> The prior art in general discloses the decay of solid precursor isotopes in a collection container in general, but does not provide adequate detail to address the inventive features of including said precursor on a rod that can operate the exposure in an open or closed configuration. The information provided in the prior art does not address these features, or provide a basis for a person of ordinary skill in the art to arrive at them without relying on improper hindsight reasoning or inappropriate claim interpretation.

EX1006, 264, 280.

32. On September 9, 2024, the Applicant filed an amendment after allowance under 37 CFR § 1.312 which amended claims 41 and 57 "to address antecedent basis issues by changing claim dependency." EX1006, 288-293. The Examiner entered the amendment in a Response to Rule 312 Communication sent

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

on September 24, 2024. EX1006, 297-299. After sending the issue notification on October 2, 2024, the USPTO issued the 603 patent on October 22, 2024. EX1006, 300-303.

C. Person of Ordinary Skill in the Art

33. A person of ordinary skill in the art at the time of the alleged invention of the 603 patent (December 5, 2019) ("POSITA") would have had a bachelor's degree in chemistry, nuclear chemistry, radiochemistry, chemical engineering, physics, or materials science, or a comparable field of study, plus approximately two to three years of professional experience with radioisotope generators, radiopharmaceutical chemistry, nuclear medicine, or other relevant industry experience. Additional graduate education could substitute for professional experience, and significant experience in the field could substitute for formal education.

D. Claim Construction

34. Below are claim constructions that, in my opinion, would have been their ordinary and customary meaning according to a POSITA (person of ordinary skill in the art in question in December 5, 2019).

1. **"disposed on the rod"** (claim 1)

35. It is my opinion that this limitation should be construed to include directly or indirectly attaching to the rod. The 603 patent specification describes attaching the isotopes indirectly to the rod using a strip or sphere:

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

> In one or more embodiments of the invention a strip or sphere is attached to the second part, which comprises means for holding the strip or sphere, such as a rod.
>
> In one or more embodiments of the invention the second part comprises a syringe, or wherein the rod is the syringe.
>
> ….
>
> The ^{212}Pb isotope source can be deposited on a strip, sphere or a rod which is made of material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers. The strip or sphere can be attached to the second part or be contained or comprised in the second parts, which comprises means for holding the strip or sphere. Such means can for example be a rod.

EX1001, 3:54-58, 8:58-65. In the 603 patent, an example of "the second part is the ^{212}Pb isotope source." EX1001, 2:31-32.

2. "wherein exposing the interior surface of the container to the precursor isotope source exposing the interior surface of the container to the precursor isotope source without having the precursor isotope source touch the interior surface." (claim 7)

36. As I explain in §VII(D), it is my opinion that the literal words of this claim are nonsensical.

37. I have been asked to consider this claim under an assumption that Patent Owner proposes that this claim should be re-written as:

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

> …wherein exposing the interior surface of the container to the precursor isotope source [***comprises***] exposing the interior surface of the container to the precursor isotope source without having the precursor isotope source touch the interior surface."

3. "allowing sufficient time for the precursor isotope source to decay comprises allowing 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours" (claim 10)

38. It is my opinion that this limitation should be construed to mean that allowing decay is inclusive and occurs for at least (*i.e.*, equal to or more than) one of the listed times.

4. "the precursor isotope source is configured to decay and emanate the one or more progeny isotopes into the container for 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours" (claim 20)

39. It is my opinion that the plain language requires the precursor isotope source must be configured such that it decays and emanates the one or more progeny isotopes for exactly 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours. *See Chef America, Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004) ("in accord with our settled practice we construe the claim as written, not as the patentees wish they had written it."). I have been asked to also consider an alternative that this limitation is construed to include a precursor isotope source that is configured such that it decays and emanates the one or more progeny isotopes for at least (or more than) one of the listed times.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

IV. GROUND 1: CLAIMS 1-8, 11-17, AND 19 ARE ANTICIPATED BY HASSFJELL-HOFF

A. Overview of Hassfjell-Hoff

40. Hassfjell-Hoff is a journal article published in 1994 and entitled "A Generator for Production of ^{212}Pb and ^{212}Bi." EX1003, 1-6. Hassfjell-Hoff was included in volume 45, number 10, of the "Applied Radiation and Isotopes" Journal (EX1003, 5 (Contents)), which was published in October 1994. EX1003, 1 (cover page); EX1004. Volume 45, number 10, of the "Applied Radiation and Isotopes" Journal was assigned ISSN 0969-8043 (EX1003, 5) and was received by the University of Wisconsin's Health Sciences Library on November 11, 1994. EX1003, 1 (cover page). As such, Hassfjell-Hoff was published and available to the public no later than November 11, 1994. EX1003, 1.

41. Hassfjell-Hoff was publicly accessible and indexed as a publication in public catalogs such as *e.g.*, the WorldCat index. EX1004. As further evidence of its public accessibility, Hassfjell-Hoff was cited in an International Patent Application directed to analogous art that published on August 23, 2001, which proves both that (i) Hassfjell-Hoff was published to those of skill in the art at least as early as that date, and (ii) which itself serves as an index for Hassfjell-Hoff. EX1005, 10:17-18; *see also* EX1015, 7:67-8:1, 13:39-41. Roy Larsen is listed as an inventor on EX1005 and EX1015. In my opinion, a POSITA would have understood that journals (e.g., EX1003) and published patent applications (e.g.,

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

EX1005) are reliable sources for information and would have been capable of accessing them well before the alleged filing date of the 603 patent. I have been informed that Hassfjell-Hoff qualifies as prior art under 35 U.S.C. §102(a).

42. Hassfjell-Hoff discloses a radioisotope generator for the production of α-emitting radionuclides. EX1003, 6. Figures 2 and 3 show the disclosed generator:

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

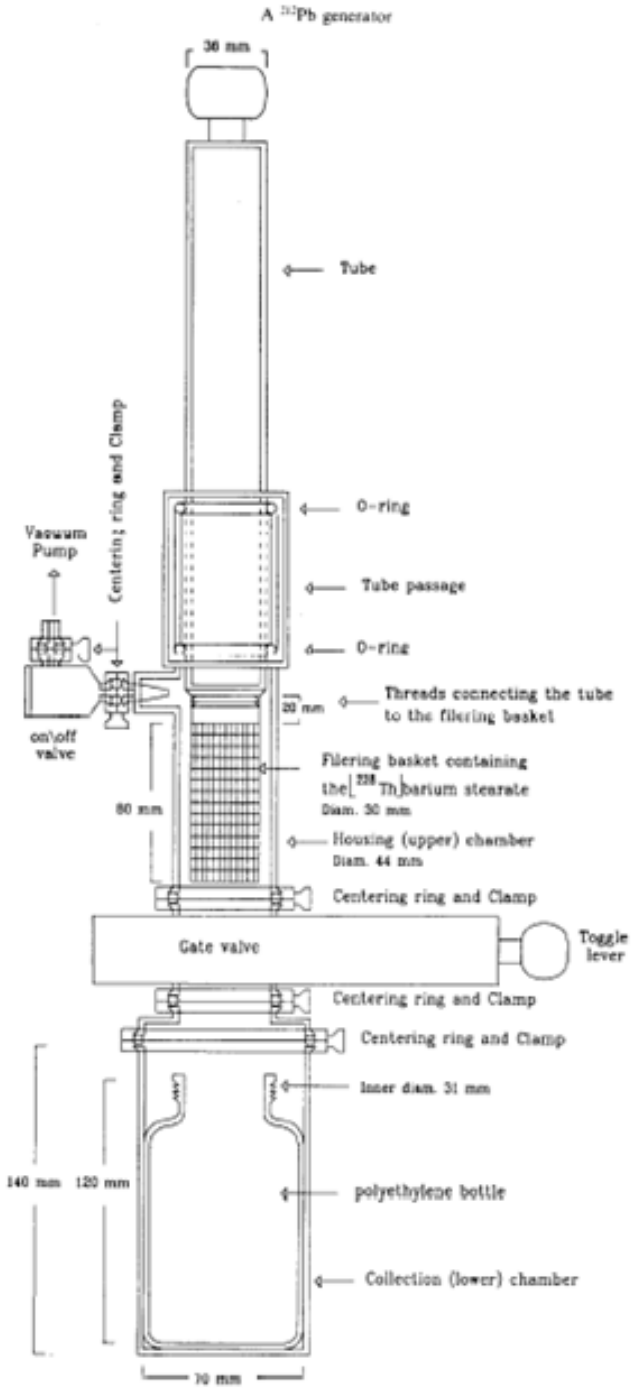


Fig. 2. The design of the generator showing functional details and operating mechanism.

EX1003, Fig. 2.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

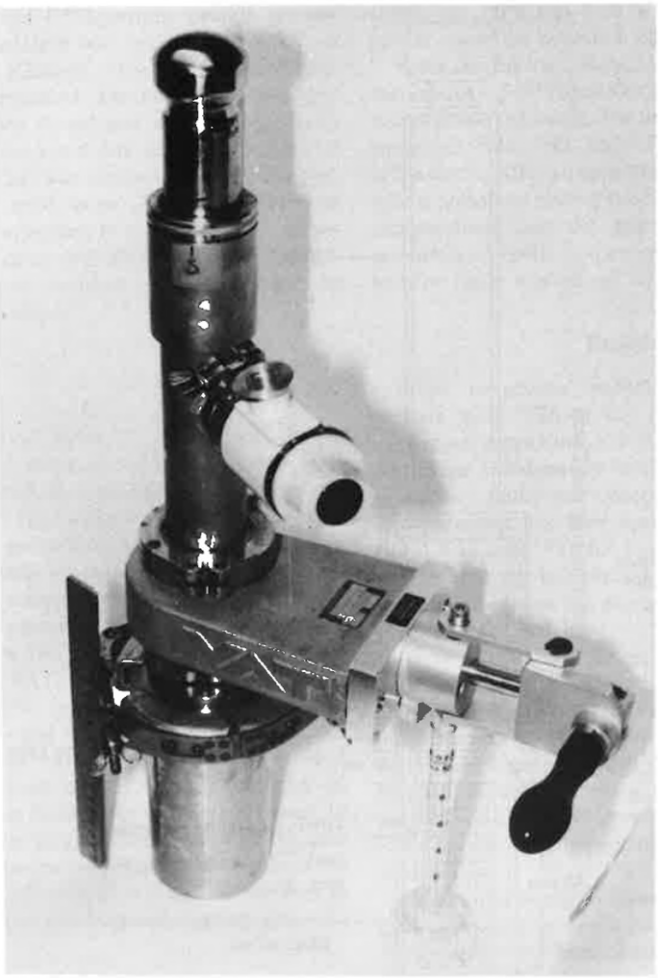


Fig. 3. A picture of the generator.

EX1003, Fig. 3. "The generator is based on the emanation of ^{220}Rn from [^{228}Th]barium stearate." EX1003, 6. The decay product of ^{220}Rn, which is ^{212}Pb, is deposited on the walls of a polyethylene bottle and can be washed off with distilled water. EX1003, 6. Hassfjell-Hoff discloses the construction of the generator shown in figures 2 and 3:

> All generator parts were made of stainless steel, and connected to standard high vacuum equipment to avoid leakage of radioactivity to the surroundings. The generator was made with

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

> two compartments, a lower compartment which is a collection chamber and an upper compartment which is a housing chamber for the source when the collection chamber is removed. These two compartments are connected via a gate valve (VAT). The packets of [^{228}Th]barium stearate are placed in a filering basket[1] mounted by threads to the end of a long tube closed in both ends…. The tube can slide on two O-rings, thus facilitating the filering basket to move between the two chambers, through the gate valve.

EX1003, 7. A "polyethylene bottle is placed inside the collection chamber" to collect the emanated ^{212}Pb. EX1003, 7. Hassfjell-Hoff discloses how the generator was operated: "When the tube is lowered, the filering basket with the emanating [^{228}Th]barium stearate becomes positioned inside the bottle. The decay products from the emanated ^{220}Rn," namely "^{212}Pb and ^{212}Bi, deposit on the walls of the bottle. After an appropriate collection time, the tube is pulled up, placing the ^{228}Th source in the upper compartment, and the gate valve is closed. The polyethylene bottle is then removed, and the radioactivity easily washed off with a suitable solution." EX1003, 7.

[1] Throughout Hassfjell-Hoff, the document refers to a "filering basket." Based on an online Norwegian-English dictionary, the meaning of the word "filering" is "a lace-like material." *See* https://glosbe.com/nb/en/Filering.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

43. The [^{228}Th]barium stearate packets are made using conventional means by taking [^{228}Th]barium stearate precipitated from a solution, filtering it onto filter membrane and washing it with methanol. EX1003, 6-7. The filter membrane with the precipitate is then folded and wrapped up into two additional filters to avoid any loss of [^{228}Th]barium stearate. EX1003, 7. The packets are then secured with plastic strips. EX1003, 7.

44. In my opinion, Hassfjell-Hoff is analogous art to the 603 patent. Hassfjell-Hoff is from the same field of endeavor as the 603 patent. They are both in the field of radioisotope generators. *See* EX1001, 1:20-27 (describing diffusion generators and methods for obtaining a container comprising ^{212}Pb radioisotope); EX1003, 6 (describing various prior art generators for obtaining ^{212}Pb by the natural decay of ^{220}Rn gas in a collection chamber). In addition, Hassfjell-Hoff is reasonably relevant to the problem the 603 patent is concerned with, as shown in my analysis below in Sections IV(B)-(Q).

45. Based on my review of the prosecution history (EX1006), Hassfjell-Hoff appears to have not been considered during prosecution of the 603 patent. EX1001, cover. Hassfjell-Hoff was cited and considered during the prosecution of related patent applications 18/680,605 ("605 application") and 18/680,372 (372 application). EX1012, 33. EX1013, 81. However, the claims of those patents are materially different from the claims of the 603 patent. For example, none of the

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

claims of the 605 application or the 372 application include a "rod" as required by the claims of the 603 patent. Yet, as I explain in detail below in Sections IV(B)-(Q), Hassfjell-Hoff discloses every element (including the rod), and therefore anticipates, claims 1-8, 11-17, and 19.

46. Hassfjell-Hoff is not cumulative of the other prior art considered during prosecution of the 603 patent. Hassfjell-2001 is a different article by the same author and was cited during prosecution of the 603 patent, however Hassfjell-2001 is materially different from Hassfjell-Hoff. *Compare* EX1003, Fig. 2 *with* EX1014, Fig. 1. Hassfjell-2001 discloses a radioisotope generator that includes a bubbler where ^{220}Rn is collected by passing dry air continuously through a cage, carrying emanated ^{220}Rn out of the cage and into a glass bubbler. EX1014, 3, Fig. 1. In contrast, Hassfjell-Hoff discloses that the generator was made with two compartments, a lower compartment which is a collection chamber and an upper compartment which is a housing chamber for the source when the collection chamber is removed. EX1003, 7.

47. Moreover, as I explain below, it was material error for the 603 patent claims to issue over Hassfjell-Hoff.

B. Claim 1

48. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

1. [1pre] A method of generating radioisotopes, the method comprising:

49. In my opinion, Hassfjell-Hoff discloses a method of generating radioisotopes. EX1003, 6-7 ("Materials and Methods").

> A generator has been developed for the production of the α-emitting radionuclide ^{212}Bi and its parent nuclide ^{212}Pb. The generator is based on the emanation of ^{220}Rn from [^{228}Th]barium stearate. The decay product of ^{220}Rn, ^{212}Pb deposits on the walls of a polyethylene bottle, and can be washed off with distilled water. The generator shows no leakage of any long-lived parent nuclides, is easy to operate and has a high degree of radiation safety.

EX1003, Abstract.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

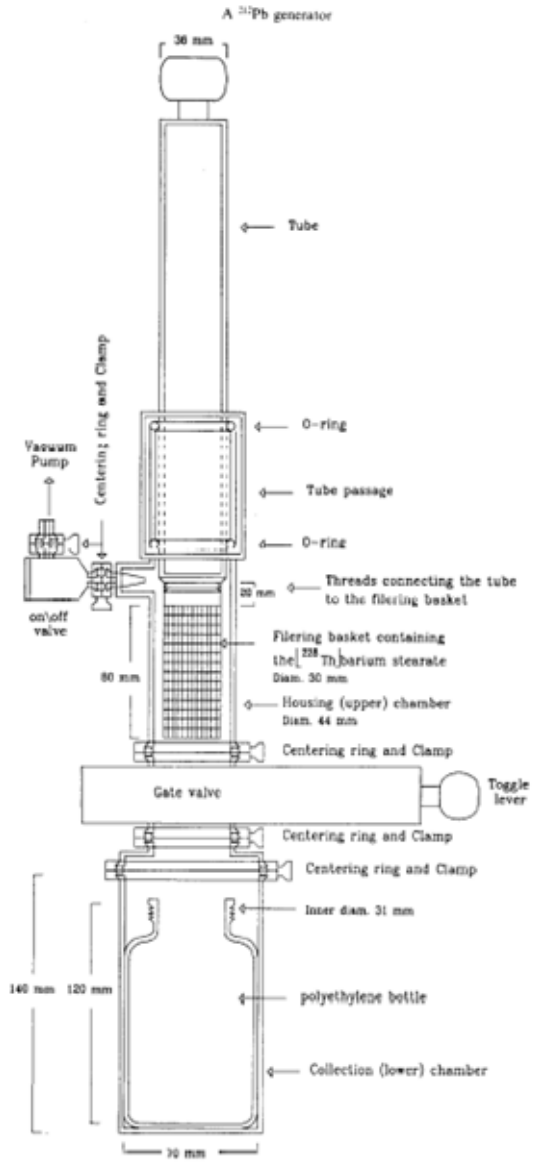


Fig. 2. The design of the generator showing functional details and operating mechanism.

EX1003, Fig. 2.

2. [1a] exposing an interior surface of a container to a precursor isotope source by sliding a rod from a closed position in which the precursor isotope source is sealed off from the interior surface of the container to an open position in which the precursor isotope source is exposed to the interior surface of the container

50. In my opinion, Hassfjell-Hoff discloses this limitation.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

51. Hassfjell-Hoff discloses that the system for producing radioisotopes includes a *precursor isotope source* (*i.e.*, packet of [^{228}Th]barium stearate). *See* EX1003, Abstract, 7, Fig. 2. Figure1 of Hassfjell-Hoff also discloses the decay mode of the ^{228}Th to the therapeutically-desired ^{212}Pb, including intermediate and subsequent isotopes.

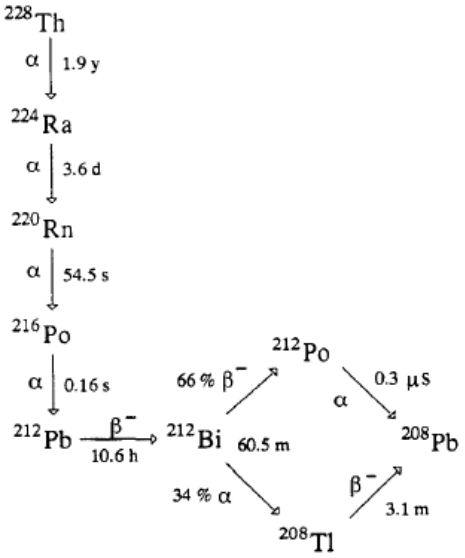


Fig. 1. The decay mode of ^{228}Th to stable ^{208}Pb.

EX1003, Fig. 1.

52. Hassfjell-Hoff discloses the operation of *exposing an interior surface of a container* (*i.e.,* the inside of the "polyethylene bottle") *to a precursor isotope source* (*i.e.*, packet of [^{228}Th]barium stearate) *by sliding a rod* (*i.e.,* tube slidably coupled to a collection chamber and a housing) *from a closed position in which the precursor isotope source is sealed off from the interior surface of the container* (*i.e.*, when the tube is pulled up and the gate valve is closed) *to an open position in*

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

which the precursor isotope source is exposed to the interior surface of the container (*i.e.*, when the gate valve is open and the tube is pushed down):

> The generator was made with two compartments, a lower compartment which is a collection chamber and an upper compartment which is a housing for the source when the collection chamber is removed. These two compartments are connected via a gate valve (VAT). The packets of [^{228}Th]barium stearate are placed in a filering basket mounted by threads to the end of a long tube closed in both ends. The filering basket has a capacity of 3-4 [^{228}Th]barium stearate packets. The tube can slide on two O-rings, thus facilitating the filering basket to move between the two chambers, through the gate valve. To neutralize pressure differences when the tube is moved, an on-off valve (VAT) with connection to a filtered air outlet is placed in the upper chamber. To collect the ^{212}Pb and ^{212}Bi, a polyethylene bottle is placed inside the collection chamber.

EX1003, 7. "When the tube is lowered, the filering basket with the emanating [^{228}Th]barium stearate becomes positioned inside the bottle. The decay products from the emanated ^{220}Rn," namely "^{212}Pb and ^{212}Bi, deposit on the walls of the bottle. After an appropriate collection time, the tube is pulled up, placing the ^{228}Th source in the upper compartment, and the gate valve is closed. The polyethylene bottle is then removed and the radioactivity easily washed off with a suitable solution." EX1003, 7.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

EX1003, 7.

53. Hassfjell-Hoff discloses exposing an interior surface of the polyethylene bottle to a precursor isotope source of [^{228}Th]barium stearate when the tube is lowered so that the filering basket becomes positioned inside the bottle. EX1003, 7. The tube/basket is lowered from a *closed position* where the ^{228}Th is not positioned inside the bottle to an *open position* where the ^{228}Th is positioned inside the bottle and exposed to the *interior surface of a container*. There is nothing in the claim or specification of the 603 patent that requires the movement of the rod to the closed position to result in a seal. Instead, claim 1 is silent as to the step in which the precursor isotope source is "*sealed off*"—it is a *comprising* claim that does not preclude additional actions being required to create the seal. Thus, in my opinion, a POSITA would have understood that Hassfjell-Hoff discloses that its rod is moved from a *closed position* where the ^{228}Th is *sealed off* to an open position by *sliding a rod*.

3. [1b] wherein the precursor isotope source is disposed on the rod

54. In my opinion, Hassfjell-Hoff discloses this limitation. *See* §III(D)(1) (construction). Hassfjell-Hoff states "The packets of [^{228}Th]barium stearate are placed in a filering basket mounted by threads to the end of a long tube closed in both ends. The filering basket has a capacity of 3-4 [^{228}Th]barium stearate packets." EX1003, 7. Thus, the packets of [^{228}Th]barium stearate, which comprise

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

the [^{228}Th]barium stearate precipitate (*i.e., precursor isotope source*) in the Hassfjell-Hoff isotope generator, are attached (*i.e.*, *disposed*) to the long tube (*i.e.*, *rod*). *See* EX1003, 7, Fig. 2. As such, Hassfjell-Hoff teaches that the *precursor isotope source is disposed on the rod*. Alternatively, and additionally, the combination of the [^{228}Th]barium stearate packets and basket is the *source* of the precursor isotope in Hassfjell-Hoff, and those are directly connected to the rod. *See* EX1003, 7, Fig. 2.

4. [1c] allowing sufficient time for the precursor isotope source to decay into one or more progeny isotopes and to emanate the one or more progeny isotopes into the container; and

55. In my opinion, Hassfjell-Hoff *discloses* this limitation. Hassfjell-Hoff states: "When the tube is lowered, the filering basket with the emanating [^{228}Th]barium stearate becomes positioned inside the bottle. The decay products from the emanated ^{220}Rn," namely "^{212}Pb and ^{212}Bi, deposit on the walls of the bottle. After an appropriate collection time, the tube is pulled up, placing the ^{228}Th source in the upper compartment, and the gate valve is closed." EX1003, 7.

56. Hassfjell-Hoff thus references a *sufficient time* (*i.e.*, an appropriate collection time) *for the precursor isotope source* (*i.e.*, the [^{228}Th]barium stearate) *to decay into one or more progeny isotopes and to emanate the one or more progeny isotopes* (*i.e.*, ^{220}Rn) *into the container* (*i.e.*, the decay products from the emanated ^{220}Rn, namely ^{212}Pb and ^{212}Bi, deposit on the walls of the bottle).

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

EX1003, 7. As such, Hassfjell-Hoff teaches allowing sufficient time for the precursor isotope source to decay into one or more progeny isotopes and to emanate the one or more progeny isotopes into the container.

5. [1d] isolating the precursor isotope source from the container by sliding the rod from the open position to the closed position.

57. In my opinion, Hassfjell-Hoff discloses this limitation. Hassfjell-Hoff teaches that *the precursor isotope source* (*i.e*., packet of [^{228}Th]barium stearate) *is isolated from the container by sliding the rod* (*i.e.*, sliding the tube slidably coupled to collection chamber) *from the open position* (*i.e.*, gate valve is open and tube is down) *to the closed position* (*i.e.*, tube is pulled up and gate valve is closed). EX1003, 7 ("After an appropriate collection time, the tube is pulled up, placing the ^{228}Th source in the upper compartment, and the gate valve is closed."), 7 ("The generator was made with two compartments, a lower compartment which is a collection chamber and an upper compartment which is a housing for the source when the collection chamber is removed."), Fig. 2.

C. Claim 2 "The method of claim 1, wherein exposing the interior surface to the precursor isotope source comprises exposing the interior surface to a thorium 228 isotope (^{228}Th) and/or a radium 224 isotope (^{224}Ra), the method further comprising allowing the ^{228}Th to decay into at least one of a radon 220 isotope (^{220}Rn) and a lead 212 isotope (^{212}Pb)."

58. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

59. As I explain above, Hassfjell-Hoff discloses *the method of claim 1*. *See* §IV(B) (claim 1).

60. Hassfjell-Hoff discloses: "When the tube is lowered, the filering basket with the emanating [^{228}Th]barium stearate becomes positioned inside the bottle. The decay products from the emanated ^{220}Rn," namely "^{212}Pb and ^{212}Bi, deposit on the walls of the bottle." EX1003, 7. Hassfjell-Hoff also discloses the overall decay chain from ^{228}Th to ^{224}Ra to ^{220}Rn to ^{216}Po to ^{212}Pb. EX1003, 7, Fig. 1. Thus, the *interior surface* of the container is exposed to ^{228}Th, which is allowed to decay into gaseous ^{220}Rn and thereafter solid ^{212}Pb.

D. Claim 3 "The method of claim 2, the method further comprising allowing the ^{212}Pb to deposit on the interior surface of the container."

61. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

62. As I explain above, Hassfjell-Hoff discloses *the method of claim 2*. *See* §§IV(B)-(C) (claims 1-2).

63. Hassfjell-Hoff discloses "The decay products from the emanated ^{220}Rn," namely "^{212}Pb and ^{212}Bi, deposit on the walls of the bottle." EX1003, 7. In my opinion, a POSITA would have understood that "the walls of the bottle" correspond to the *interior surface of the container*.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

E. Claim 4 "The method of claim 1, wherein isolating the precursor isotope source from the container further comprises withdrawing the precursor isotope source into a chamber having a gas tight seal."

64. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

65. As I explain above, Hassfjell-Hoff discloses *the method of claim 1*. *See* §IV(B) (claim 1).

66. Hassfjell-Hoff discloses:

> The generator was made with two compartments, a lower compartment which is a collection chamber and an upper compartment which is a housing for the source when the collection chamber is removed. These two compartments are connected via a gate valve (VAT).

EX1003, 7.

67. The generator is "connected to standard high vacuum equipment to avoid leakage of radioactivity to the surroundings." EX1003, 7. Hassfjell-Hoff further discloses "After an appropriate collection time, the tube is pulled up, placing the ^{228}Th source in the upper compartment, and the gate valve is closed." EX1003, 7. Thus, the tube on which the precursor isotope is disposed is pulled up (*i.e.*, the precursor isotope source is withdrawn) into the upper compartment. Also, Hassfjell-Hoff discloses that "Despite the relatively strong ^{228}Th source, no detectable leakage of any kind of radioactivity out of the generator has been

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

observed." EX1003, 7. Because a radiation leak would occur via emanated gaseous ^{220}Rn, in my opinion a POSITA would have understood that closing the gate valve forms a *gas tight seal* between the upper compartment (*i.e.*, the housing *chamber*) and the lower compartment (*i.e.*, the collection *chamber*).

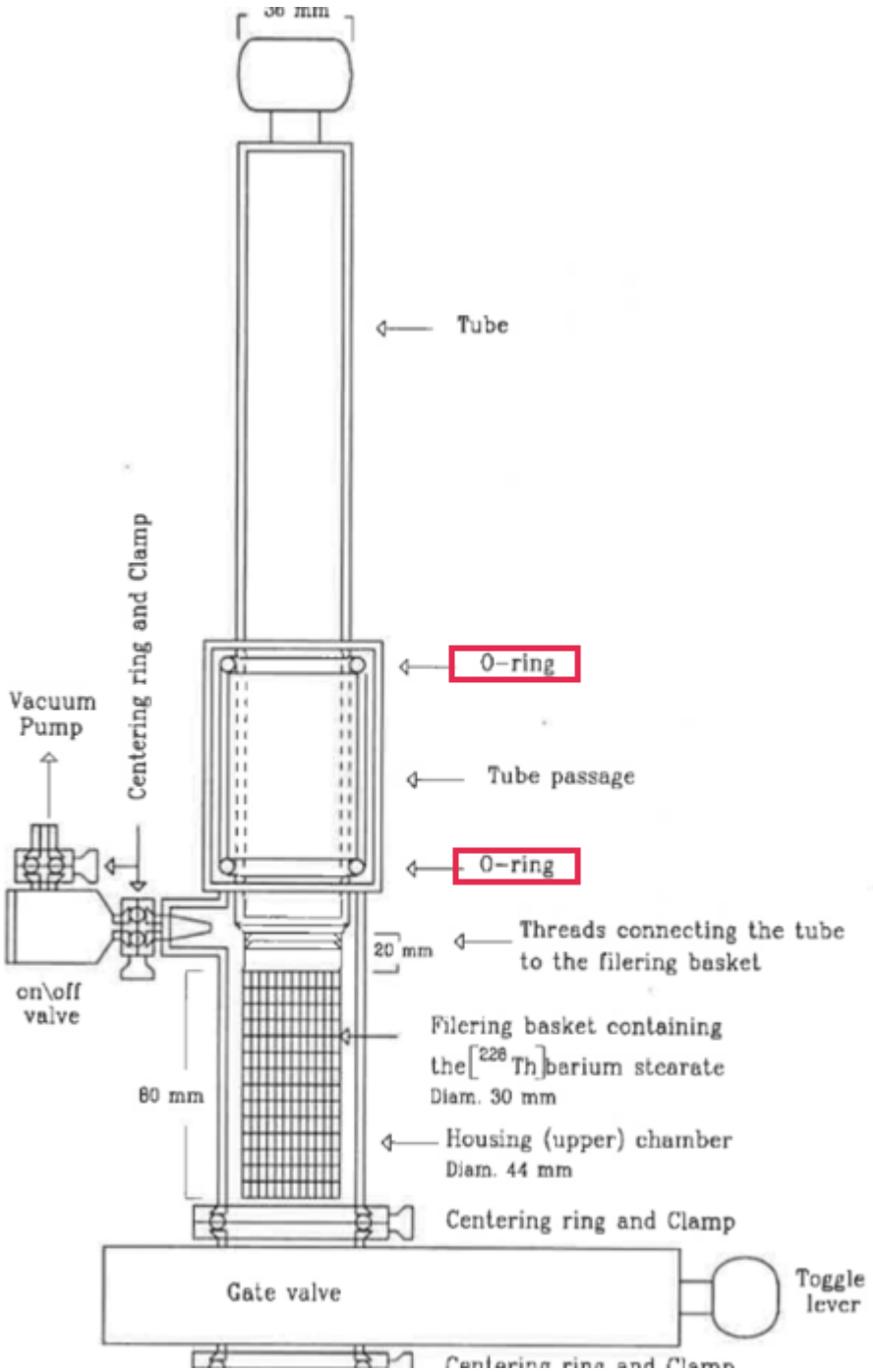
F. Claim 5 "The method of claim 4, wherein withdrawing the precursor isotope source into a gas tight seal comprises sealing the rod within a tube using an O-ring to form the gas tight seal between the rod and the tube."

68. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

69. As I explain above, Hassfjell-Hoff discloses *the method of claim 4*. *See* §§IV(B), (E) (claims 1, 4).

70. As shown below in Figure 2, Hassfjell-Hoff's tube extends through a larger-diameter tube passage that extends from the top end of the upper chamber. Hassfjell-Hoff discloses two O-rings interposed against the exterior surface of the tube and an interior surface of a larger-diameter tube passage. See EX1003, 7, Fig. 2. Hassfjell-Hoff's O-rings permit the lower end of the tube to slide axially through the upper chamber and into the collection chamber, while sealing the space defined between the tube's exterior surface and the larger-diameter tube passage's interior surface. Being attached to the lower end of the tube, the filering basket containing the [228Th]barium stearate moves with the tube from an "up" position to a "lowered" position. EX1003, 7.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642



EX1003, Fig. 2 (excerpt).

71. When Hassfjell-Hoff's tube is set in the "up" position, the filering basket containing the [^{228}Th]barium stearate is withdrawn inside the housing

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

(upper) chamber. EX1003, Fig. 2. Hassfjell-Hoff discloses that the O-ring forms a gas-tight seal. EX1003, Abstract ("The generator shows no leakage of any long-lived parent nuclides, is easy to operate and has a high degree of radiation safety."), 6 ("enclosing the [^{228}Th]barium stearate in a gas-tight collection chamber" was the known "simpler and better approach to collect[ion]." In my opinion, a POSITA would have understood that *sealing the rod within a tube using an O-ring to form the gas tight seal between the rod and the tub*e was necessary to prevent the escape of any gas from the chamber containing the filering basket that contains ^{228}Th and which emanates gaseous ^{220}Rn. For example, Hassfjell-Hoff describes that it is known to enclose [^{228}Th]barium stearate in a gas-tight collection chamber in order to collect ^{212}Pb and ^{212}Bi. EX1003, 6. In my opinion, a POSITA would have understood that if the O-ring of Hassfjell-Hoff did not form a gas-tight seal, then at least some gaseous ^{220}Rn would diffuse past the space between the tube passage and the tube, creating unacceptable risks for any person in the vicinity of the radioisotope generator. EX1003, Fig. 2. In my opinion, a POSITA would have understood that the O-ring forms a gas tight seal because "Despite the relatively strong ^{228}Th source, no detectable leakage of any kind of radioactivity out of the generator has been observed." EX1003, 7.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

G. Claim 6 "The method of claim 1, the method further comprising turning the container before exposing the interior surface to the precursor isotope."

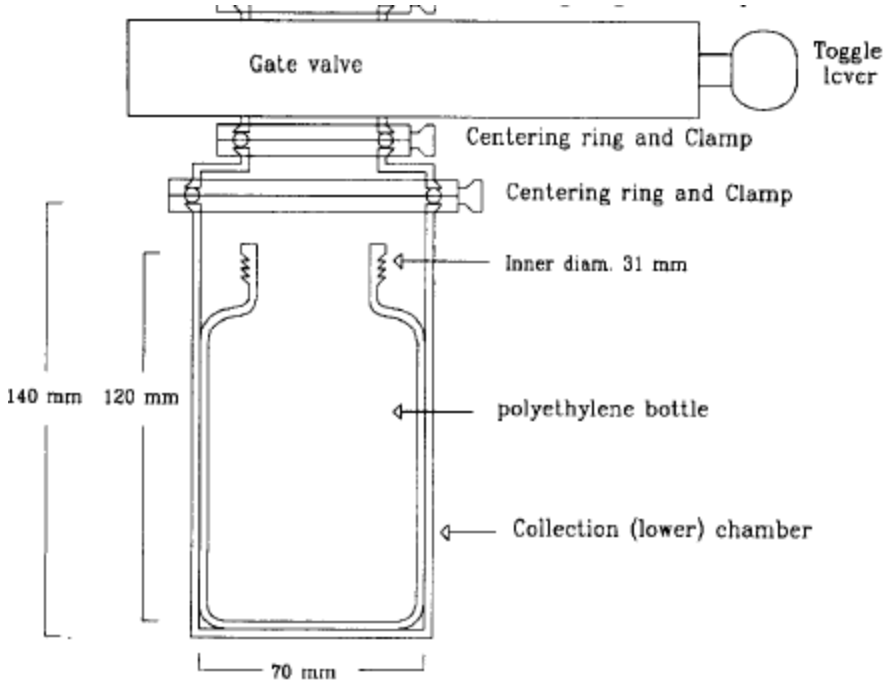
72. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

73. As I explain above, Hassfjell-Hoff discloses *the method of claim 1*. *See* §IV(B) (claim 1).

74. Because this claim requires turning the container before exposing the interior surface, the 603 patent disclosure of picking up the bottle and turning it before putting on its cap corresponds to this claim. *See* EX1001, 9:58-64, 109:7-19, 10:41-44 (depicting how the screw caps are removed from the containers by unscrewing them).

75. This claim limitation is so broad that it covers a technician at any time before placing Hassfjell's bottle in the collection chamber: removing the bottle's lid (turning a bottle relative to a lid), rotating the bottle when placing it on a shelf, rotating the bottle when removing it from the box, or rotating the bottle during bottle manufacture. Hassfjell-Hoff does not explicitly disclose that the method further comprises the step of turning the container before exposing the interior surface (of the container) to the precursor isotope. However, Hassfjell-Hoff depicts that the container is a polyethylene bottle:

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642



EX1003, 8, Fig. 2.

76. Figure 2 shows the bottle is a polyethylene bottle that has threads at the top and which has an inner diameter of 31 mm. EX1003, Fig. 2. In my opinion, a POSITA would have understood that the bottle is round (by virtue of it having a diameter) and is intended to be affixed to other articles (*e.g.*, a lid, etc.) by being *turned* and thereby screwed to whichever article is to be used. In my opinion, a POSITA would have understood that the polyethylene bottle would have had a lid on it before use to ensure that no contaminants are in the bottle before use. Because the container relative to its lid must be *turned* (for example, to remove the lid) *before* being placed within the collection (lower) chamber depicted by Hassfjell-Hoff, this limitation is disclosed.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

H. Claim 7 "The method of claim 1, wherein exposing the interior surface of the container to the precursor isotope source exposing the interior surface of the container to the precursor isotope source without having the precursor isotope source touch the interior surface."

77. As explained in §VII(D), in my opinion, this claim is indefinite and nonsensical.

78. In this section, I have been asked to address this claim under an alternative that assumes patent owner rewrites the claim in claim construction. *See* §III(D)(2) (construction).

79. In my opinion, Hassfjell-Hoff discloses this claim (under the assumption that the claim is rewritten) arranged as claimed and in an enabling manner.

80. As I explain above, Hassfjell-Hoff discloses *the method of claim 1*. *See* §IV(B) (claim 1).

81. Figure 2 discloses that, based on the dimensions shown, the radioisotope generator is designed to prevent the precursor isotope source from touching the interior surface:

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

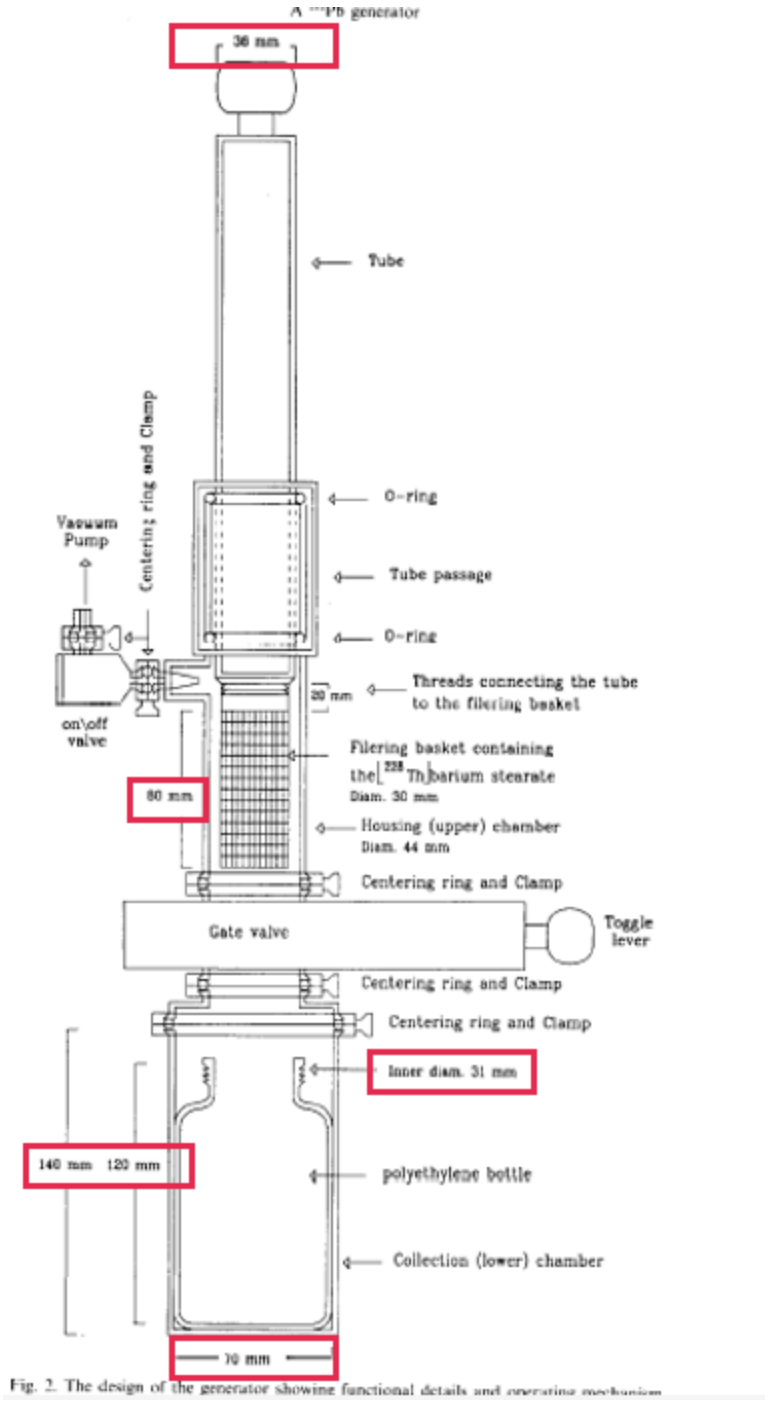


Fig. 2. The design of the generator showing functional details and operating mechanism

EX1003, Fig 2.

82. Figure 2 of Hassfjell-Hoff depicts that the filering basket is connected to the rod (*i.e.*, tube) by threads. EX1003, Fig. 2. The threads are positioned at the

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

bottom end of the tube. EX1003, Fig. 2. The tube has a diameter of 36 mm based on the label on the handle that is at the top of the tube. EX1003, Fig. 2. The inner diameter of the mouth of the polyethylene bottle is 31mm. EX1003, Fig. 2. The filering basket containing the [^{228}Th]barium stearate has a diameter of 30 mm and a height of 80 mm, and the polyethylene bottle has a height of 120 mm. EX1003, Fig. 2. Based on these dimensions, when the tube is pushed down to lower the filering basket the diameter of the filering basket (*i.e.*, 30mm) is smaller than the inner diameter of the neck of the polyethylene bottle (*i.e.*, 31mm). EX1003, Fig. 2. The tube slides on two O-rings, which are described in Figure 2 as "centering rings." EX1003, 7, Fig. 2. As shown in Hassfjell-Hoff, the polyethylene bottle is held in the center of the collection (lower) chamber which prevents it from moving side to side. EX1003, Fig. 2. The tube passage and O-rings are aligned by the housing with the centering ring and clamp, gate valve, and the collection (lower) chamber. EX1003, Fig. 2. In my opinion, a POSITA would have understood that the disclosure of the "centering ring and clamp" and the inner diameter of the neck of the polyethylene bottle (31 mm) that is greater than the diameter of the filering basket (30 mm) signifies that the filering basket is able to enter the polyethylene bottle without touching the sides. Also, in my opinion, a POSITA would have understood that the filering basket will stop being lowered at the neck of the bottle before touching the bottom of the polyethylene bottle. The filering basket has a

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

height of 80 mm which is shorter than the 120 mm height of the polyethylene bottle and a diameter of 30 mm which is smaller than the 70 mm diameter of the polyethylene bottle and the 31 mm inside diameter of the neck of the polyethylene bottle. EX1003, Fig. 2. In addition, in my opinion, a POSITA would have understood that the purity of the emanated ^{212}Pb is ensured by preventing the precursor isotope source from touching the interior surface of the container. EX1003, Fig. 2. Taken together, this discloses the claim feature where the precursor isotope source (*i.e.*, the [^{228}Th]barium stearate contained in the filering basket) does not touch any interior surface of the container (*i.e.*, any interior wall or the bottom of the polyethylene bottle).

I. Claim 8 "The method of claim 1, wherein allowing sufficient time for the at least one progeny isotopes to emanate into the container comprises allowing the at least one progeny isotopes to emanate into the container from the precursor isotope source through a gas permeable barrier."

83. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

84. As I explain above, Hassfjell-Hoff discloses *the method of claim 1*. *See* §IV(B) (claim 1).

85. Hassfjell-Hoff discloses *allowing sufficient time for the at least one progeny isotopes to emanate into the container*. *See* §IV(B)(4) (limitation 1c). Specifically, Hassfjell-Hoff discloses that this is accomplished by *allowing the at*

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

least one progeny isotopes to emanate into the container from the precursor isotope source through a gas permeable barrier: "The packets of [^{228}Th]barium stearate are placed in a filering basket mounted by threads to the end of a long tube closed in both ends. The filering basket has a capacity of 3-4 [^{228}Th]barium stearate packets.... When the tube is lowered, the filering basket with the emanating [^{228}Th]barium stearate becomes positioned inside the bottle. The decay products from the emanated ^{220}Rn," namely ^{212}Pb and ^{212}Bi, deposit on the walls of the bottle. EX1003, 7.

86. The at least one progeny isotopes (*i.e.*, ^{220}Rn) are allowed to *emanate into the container* through the filering basket and the packet filter material (either or both of which are *a gas permeable barrier*). This emanation enables the lead-212 to "deposit on the walls of the bottle." According to Hassfjell-Hoff, Rn emanation is "well-known." EX1003, 6. According to Hassfjell-Hoff, "^{220}Rn has a relatively short diffusion distance at room temperature and atmospheric pressure," and ^{212}Pb and ^{212}Bi can be collected "by enclosing the [^{228}Th]barium stearate in a gas-tight collection chamber." EX1003, 6. In my opinion, a POSITA would have understood Hassfjell-Hoff to disclose that the emanation happens for a *sufficient time for the precursor isotope source to decay into one or more progeny isotopes and to emanate the one or more progeny isotopes into the container.*

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

J. Claim 11 "The method of claim 1, the method further comprising changing an orientation of the container before exposing the interior surface to the precursor isotope."

87. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

88. As I explain above, Hassfjell-Hoff discloses *the method of claim 1*. *See* §IV(B) (claim 1).

89. The *interior surface* refers to the interior surface of the container. *See* §IV(B)(2) (limitation 1a); §IV(C) (claim 2). As explained in claim 6, this claim limitation is so broad that it covers a technician at any time before placing the bottle in the collection chamber: removing the bottle's lid (turning a bottle relative to a lid), rotating the bottle when placing it on a shelf, rotating the bottle when removing it from the box, or rotating the bottle during bottle manufacture. §IV(G) (claim 6). In my opinion, a POSITA would have understood that turning the bottle constitutes *changing an orientation*, specifically the angular orientation.

K. Claim 12

90. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

1. [12pre] A system for generating radioisotopes, the system comprising

91. In my opinion, Hassfjell-Hoff discloses the preamble. *See* §IV(B)(1) (limitation 1pre). Hassfjell-Hoff discloses that radioisotope generation was performed using the depicted system. EX1003, 7.

2. [12a] a precursor isotope source disposed on a rod, the rod configured to slide between an open position in which the precursor isotope is exposed to an interior surface of a container to allow the precursor isotope source to decay into one or more progeny isotopes emanated into the container, and

92. In my opinion, Hassfjell-Hoff discloses this limitation. *See* §IV(B)(2) (limitation 1a). In Figure 2 of Hassfjell-Hoff, the precursor isotope source (*i.e.*, packet of [^{228}Th]barium stearate) is disposed on the end of a tube (*i.e.*, on a rod) inside a basket (*see* §IV(B)(3) (limitation 1b)), and the tube (*i.e.*, rod) is configured to slide between an open position in which the precursor isotope is exposed to an interior surface of a container to allow the precursor isotope source to decay (see §IV(B)(2) (limitation 1a)). EX1003, 6-7, Fig. 2. Hassfjell-Hoff also describes that the precursor isotope source *decays into one or more progeny isotopes that emanate into the container* (*i.e.*, polyethylene bottle in Figure 2). *See* §IV(B)(4) (limitation 1c).

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

3. [12b] a closed position in which the precursor isotope source is sealed off from the container to isolate the precursor isotope source from the interior surface.

93. In my opinion, Hassfjell-Hoff discloses this limitation. Hassfjell-Hoff's tube is configured to slide to a closed position in which the *precursor isotope source* (*i.e*., packet of [228Th]barium stearate) is sealed off from the container to isolate the precursor isotope source from the interior surface. EX1003, 7; §IV(B)(5) (limitation 1d). Figure 2 shows that if the tube is pulled upwards and the gate valve is closed, the precursor isotope source is *sealed off from the* polyethylene bottle in the collection (lower) chamber. EX1003, 7, Fig. 2; §IV(B)(2) (limitation 1a). As I point out above in Claim 5, in addition to sealing gas leak, the purpose of the O-rings are also to keep the basket true relative to other jacket, so that the basket could be lowered to the collection bottle without touching it. §IV(F) (claim 5).

L. Claim 13 "The system of claim 12, wherein the precursor isotope source comprises a thorium 228 isotope (^{228}Th) and/or a radium 224 isotope (^{224}Ra), the one or more progeny isotopes comprising at least one of a radon 220 isotope (^{220}Rn) and a lead 212 isotope (^{212}Pb)."

94. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

95. As I explain above, Hassfjell-Hoff discloses *the system of claim 12*. *See* §IV(K) (claim 12).

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

96. Hassfjell-Hoff discloses: "When the tube is lowered, the filering basket with the emanating [^{228}Th]barium stearate becomes positioned inside the bottle. The decay products from the emanated ^{220}Rn," namely "^{212}Pb and ^{212}Bi, deposit on the walls of the bottle." EX1003, 7.

97. In my opinion, a POSITA would have understood that [^{228}Th]barium stearate is the claimed thorium-228 isotope (^{228}Th). Thus, the interior surface of the container is exposed to ^{228}Th (*i.e.*, the *precursor isotope source*), which decays into (*i.e.*, becomes *progeny isotopes*) ^{220}Rn and ^{212}Pb. EX1003, 7.

M. Claim 14 "The system of claim 12, wherein, in the closed position, the rod forms a gas tight seal with a tube in which the rod slides to isolate the precursor isotope source from the interior surface."

98. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner. *See* §IV(F) (claim 5).

99. As I explain above, Hassfjell-Hoff discloses *the system of claim 12*. *See* §IV(K) (claim 12).

100. According to Hassfjell-Hoff, there is an O-ring that surrounds the tube (*i.e.*, *rod*) and is positioned between that tube and the surrounding tube passage (*i.e., tube in which the rod slides*). EX1003, Fig. 2. Hassfjell-Hoff also discloses that "no detectable leakage of any kind of radioactivity out of the generator has been observed." EX1003, 7.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

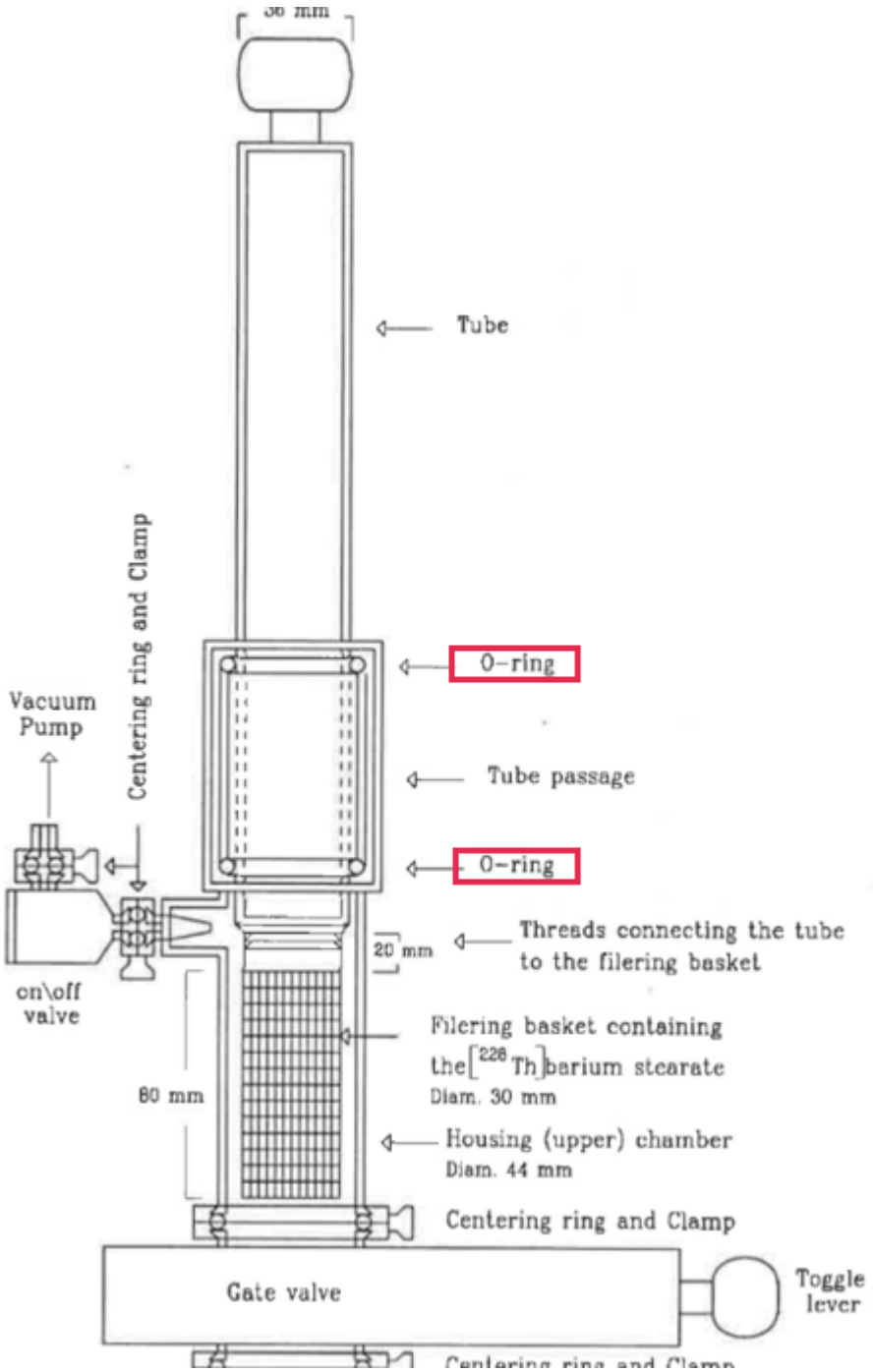
N. Claim 15 "The system of claim 14, wherein the rod includes at least one O-ring to form the gas tight seal with the tube in the closed position."

101. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

102. As I explain above, Hassfjell-Hoff discloses *the system of claim 14*. *See* §§IV(K), (M) (claims 12, 14).

103. The top chamber has O-ring seals to keep the system gas tight. *See* EX1003, Fig. 2; §IV(F) (claim 5). As shown in Figure 2, at least two O-rings are present between the tube (the *rod*) and the tube passage (the *tube*). EX1003, Fig. 2. When in the closed position, no gas can escape through the O-ring. EX1003, 7 (there was "no detectable leakage of any kind of radioactivity out of the generator…").

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642



EX1003, Fig. 2 (excerpt).

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

O. Claim 16 "The system of claim 12, wherein the rod holds the precursor isotope source without having the precursor isotope source touch the interior surface."

104. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

105. As I explain above, Hassfjell-Hoff discloses *the system of claim 12*. *See* §IV(K) (claim 12).

106. *The rod holds the precursor isotope source*. *See* §IV(B)(3) (limitation 1b). The system operates *without having the precursor isotope source touch the interior surface*. *See* §IV(H) (claim 7).

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

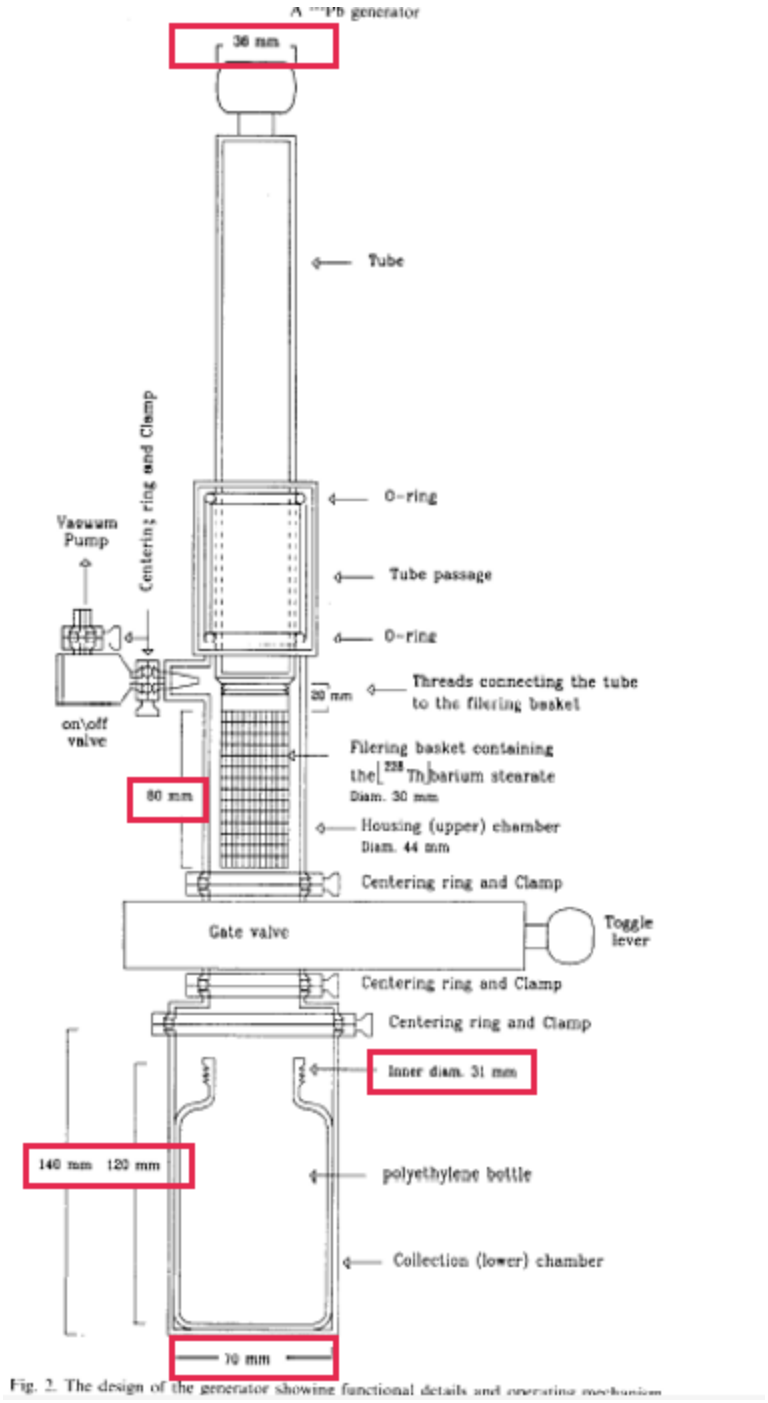


Fig. 2. The design of the generator showing functional details and operating mechanism

EX1003, Fig. 2. As shown in Figure 2 of Hassfjell-Hoff, lowering the tube moves the filering basket through the gate valve and into the polyethylene bottle. EX1003, Fig. 2. When this occurs, the filering basket will be positioned in the center of the

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

polyethylene bottle. EX1003, Fig. 2 (showing multiple "centering ring and clamp"). *See also* §IV(H) (claim 7). In my opinion, a POSITA would have understood that the positioning of the filering basket, which contains the [^{228}Th]barium stearate (*i.e.*, the precursor isotope source), at the center of the polyethylene bottle means that the rod holds the precursor isotope source without having the precursor isotope source touch the interior surface of the of the container. *See* EX1003, Fig. 2.

P. Claim 17 "The system of claim 12, wherein the precursor isotope source is encapsulated in a gas permeable barrier."

107. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

108. As I explain above, Hassfjell-Hoff discloses *the system of claim 12*. *See* §IV(K) (claim 12).

109. The filering basket and the packet are each *a gas permeable barrier*. *See* §IV(I) (claim 8). Each of the filering basket and the packet *encapsulates the precursor isotope source*. EX1003, 7 ("The filter membrane with the precipitate was folded and wrapped up in two additional filter to avoid any loss of [^{228}Th]barium stearate….The packets of [^{228}Th]barium stearate are placed in a filering basket").

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Q. Claim 19 "The system of claim 13, further comprising the container, wherein the interior surface of the container is configured to allow the ^{212}Pb to deposit on the interior surface."

110. In my opinion, Hassfjell-Hoff discloses this claim arranged as claimed and in an enabling manner.

111. As I explain above, Hassfjell-Hoff discloses *the system of claim 13*. *See* §§IV(K)-(L) (claims 12, 13).

112. Hassfjell-Hoff discloses "The decay products from the emanated ^{220}Rn," namely "^{212}Pb and ^{212}Bi, deposit on the walls of the bottle." EX1003, 7. The walls of the bottle are the interior surface of the container. *See* §IV(B)(2) (limitation 1a).

V. GROUND 2: CLAIMS 5-7, 10-11, 15-16, AND 20 ARE OBVIOUS OVER HASSFJELL-HOFF

A. Overview of Hassfjell-Hoff

113. My explanation of the Hassfjell-Hoff reference is above and incorporated here by reference into Ground 2. *See* §IV(A).

B. Claim 5 "The method of claim 4, wherein withdrawing the precursor isotope source into a gas tight seal comprises sealing the rod within a tube using an O-ring to form the gas tight seal between the rod and the tube."

114. As explained above, this limitation is disclosed by Hassfjell-Hoff. *See* §IV(F) (claim 5). Moreover, in my opinion, this claim would have been obvious to a POSITA because such a feature would have been necessary to prevent the escape of any gas from the chamber containing the filering basket that contains ^{228}Th and

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

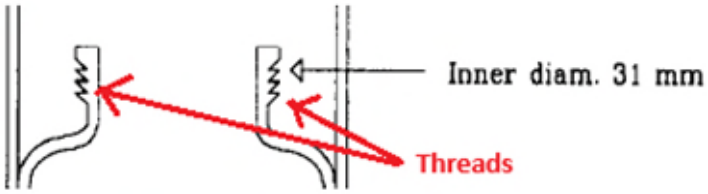
which emanates gaseous ^{220}Rn. For example, Hassfjell-Hoff states that all of the generator parts were "connected to standard high vacuum equipment to avoid leakage of radioactivity to the surroundings." EX1003, 7. Furthermore, Hassfjell-Hoff states that "Despite the relatively strong ^{228}Th source, no detectable leakage of any kind of radioactivity out of the generator has been observed." EX1003, 7. It is also my opinion that a POSITA would have understood that O-rings are commonly used in many fields to provide gas-tight seals between concentrically arranged tubes. *See* EX1016, 1 (describing advantages of O-ring seals for preventing undesirable loss of a fluid or gas and defining dynamic applications where the parts to be sealed move relative to one another, such as O-rings installed on pistons or rods), 14 (describing that O-rings can be used as rod seals), 39 (depicting a rod seal where the O-ring is assembled in the outside element, *i.e.*, tube). Finally, Hassfjell-Hoff describes that it is known to enclose [^{228}Th]barium stearate in a gas-tight collection chamber in order to collect ^{212}Pb and ^{212}Bi. EX1003, 6. In my opinion, doing so would have been within the skill and knowledge of a POSITA, would have led to predictable results, would have created a reasonable expectation of success, would have been compatible with Hassfjell-Hoff, and would have been a mere design choice. Motivation to do so arises from the desire and imperative to ensure that the radioactive materials are controlled and

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

do not escape from the radioisotope generators. In my opinion, such motivations would have been a matter of common sense and known to a POSITA.

C. Claim 6 "The method of claim 1, the method further comprising turning the container before exposing the interior surface to the precursor isotope."

115. As explained above, this limitation is disclosed by Hassfjell-Hoff because it is so broad that it covers actions of a technician at any time before placing the bottle in the collection chamber. *See* §IV(G) (claim 6). Moreover, in my opinion, this claim would have been obvious to a POSITA because to turn the container before exposing the interior surface to the precursor isotope is part of the design of the container itself in Hassfjell-Hoff. Figure 2 depicts that there are threads around the neck of the polyethylene bottle (container) as shown below:



EX1003, Fig. 2.

116. In my opinion, a POSITA would have appreciated that threads facilitate and encourage the bottle to be unscrewed or screwed (*e.g.*, from a lid) before a user places the bottle within the collection (lower) chamber of Hassfjell-Hoff. Furthermore, in my opinion, a POSITA would have known to provide containers with lids so that the containers can be sterilized prior to use, or can be

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

sterilized after use, or can be sealed to ensure the integrity of the contents. *See* EX1003, 6 (describing various prior art generators for radiation therapy). Doing so would have been desirable to ensure that the container could be sterilized either before or after use, or to seal the container to ensure the integrity of the contents of the container, and this would have been within the skill and knowledge of a POSITA, would have led to predictable results, would have created a reasonable expectation of success, would have been compatible with Hassfjell-Hoff, and would have been a mere design choice.

D. Claim 7 "The method of claim 1, wherein exposing the interior surface of the container to the precursor isotope source [sic] exposing the interior surface of the container to the precursor isotope source without having the precursor isotope source touch the interior surface."

117. As explained above and below, this limitation is nonsensical or disclosed by Hassfjell-Hoff. *See* §IV(H) (claim 7); §VII(D). Moreover, in my opinion, this claim would have been obvious to a POSITA because Hassfjell-Hoff states that gaseous ^{220}Rn has a "relatively short" diffusion distance at room temperature and atmospheric pressure. EX1003, 6. Hassfjell-Hoff also states that it is known to fill the volume of a collection chamber with ^{220}Rn gas so that when the ^{220}Rn decays, the resultant ^{212}Pb will deposit on the walls of a collection chamber. EX1003, 6. Thus, it would be obvious to a POSITA that the interior surface of the container (*i.e.*, the polyethylene bottle) should be exposed to the precursor isotope

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

such that only the ^{220}Rn gas should emanate, thus meaning that the precursor isotope source (*i.e.*, ^{228}Th) does not touch the interior surface of the container. Doing so would have been within the skill and knowledge of a POSITA, would have led to predictable results, would have created a reasonable expectation of success, and would have been compatible with Hassfjell-Hoff. In my opinion, a POSITA would have been motivated to do so because doing so would prevent the contamination of the interior surface of the container with ^{228}Th particles that could otherwise lead to radiation safety problems due to the 1.9 year half-life of ^{228}Th. Such motivations would have been a matter of common sense and known to a POSITA.

E. Claim 10 "The method of claim 1, wherein allowing sufficient time for the precursor isotope source to decay comprises allowing 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours."

118. In my opinion, Hassfjell-Hoff renders this claim obvious. *See* §III(D)(3) (claim 10 construction).

119. As I explain above, Hassfjell-Hoff discloses *the method of claim 1*. *See* §IV(B) (claim 1).

120. Hassfjell-Hoff explicitly discloses that "Filter membrane packets with [^{228}Th]barium stearate with ^{228}Th at the kBq level have shown unchanged emanation ability for ^{220}Rn during 1 yr…The generator has been operated with 40-50MBq (1.1-1.4mCi) of ^{228}Th for 1 yr, and the total amount of ^{212}Pb that can be

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

collected inside the polyethylene bottle at saturation has decreased from 50 to 11% of the ^{228}Th radioactivity." EX1003, 7. A POSITA would recognize that this means that the generator was operated for "sufficient time" to allow the "precursor isotope source to decay" that included at least 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours. *See* §III(D)(3) (claim 10 construction). A POSITA would have understood that the 10.6 hour half-life of ^{212}Pb would have meant that, after 10.6 hours of collection, the amount of ^{212}Pb would be about 50% the maximum expected to exist. Thus, allowing the system to emanate for 10.6 hours would have been obvious to try. In my opinion, a POSITA would have understood that selection of the exact time was a matter of routine optimization. I discuss below, in Section VI(D), how the selection of the exact time was well-known and would have included "sufficient time" to allow the "precursor isotope source to decay" that included at least 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours. *See* §VI(D) (claim 10); EX1007, Fig. 4, [0030].

121. Hassfjell-Hoff also describes conventional systems that have operating times that meet the claimed invention. *See generally* EX1003, 6. In one example, generators based on ^{224}Ra were constructed that operated for 1-2 weeks based on the 3.7 day half-life of ^{224}Ra. EX1003, 6. In my opinion, a POSITA would have recognized and been familiar with each of these prior art systems that were disclosed by Hassfjell-Hoff, and would also have understood that during their

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

operation the ^{228}Th was allowed to decay for 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours based on the generator being used for at least those times. Thus, it would have been obvious to a POSITA to permit the precursor isotope source to decay for at least about 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours thereby forming the claimed progeny isotopes. Motivation to allow this amount of time for decay arises from the need to collect sufficient radioisotopes and is understood in the art as dependent on the half-lives of the precursor isotope sources. EX1007, Fig. 4, [0030]. In my opinion, a POSITA would have understood that selection of the exact time was a matter of routine optimization.

F. Claim 11 "The method of claim 1, the method further comprising changing an orientation of the container before exposing the interior surface to the precursor isotope."

122. As explained above, this limitation is disclosed by Hassfjell-Hoff because it is so broad that it covers actions of a technician at any time before placing the bottle in the collection chamber. *See* §IV(J) (claim 11). Moreover, in my opinion, this claim would have been obvious to a POSITA because the most efficient way to open a bottle is to unscrew the cap from that bottle, thereby changing the bottle's angular orientation during that step. *See* EX1003, Fig. 2 (showing that the polyethylene bottle that corresponds to the claimed container has threads at the top which are designed to screw the bottle and/or a cap to the bottle

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

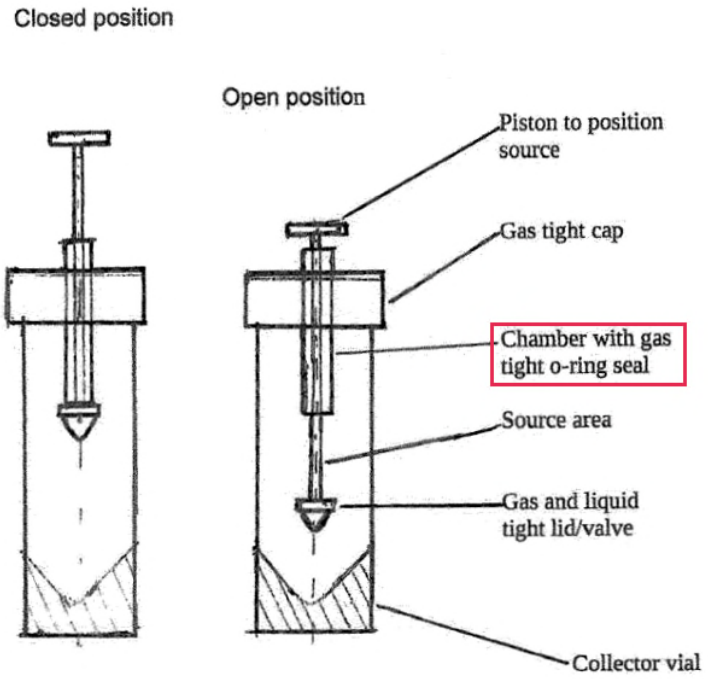
and/or the bottle to another threaded orifice). In my opinion, a POSITA would also have understood that bottles are provided with caps. Thus, in Figure 2 of Hassfjell-Hoff where the polyethylene bottle does not have a cap, it is my opinion that a POSITA would have understood and expected that the bottle would have had a corresponding cap. EX1003, Fig. 2. It would therefore be obvious to unscrew the cap before inserting the bottle into the radioisotope generator shown by Hassfjell-Hoff in Fig. 2. It is also obvious that the bottle will have been manufactured and transported, and that those actions would comprise changing the angular orientation (*i.e.*, turning it). This means that the step of changing the orientation of the container before exposing the interior surface to the precursor isotope would have been obvious because the bottle (*i.e., container*) would have been turned before inserting it into the collection (lower) chamber. EX1003, Fig. 2. Changing an orientation of the container before exposing the interior surface to the precursor isotope would have been within the skill and knowledge of a POSITA, would have led to predictable results, and would have created a reasonable expectation of success, would have been compatible with Hassfjell-Hoff, and would have been a mere design choice. Motivation to do so arises from a POSITA's knowledge regarding how to work with bottles (*e.g.,* make bottles or remove the caps from bottles). Such motivations would have been a matter of common sense and known to a POSITA.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

G. Claim 15 "The system of claim 14, wherein the rod includes at least one O-ring to form the gas tight seal with the tube in the closed position."

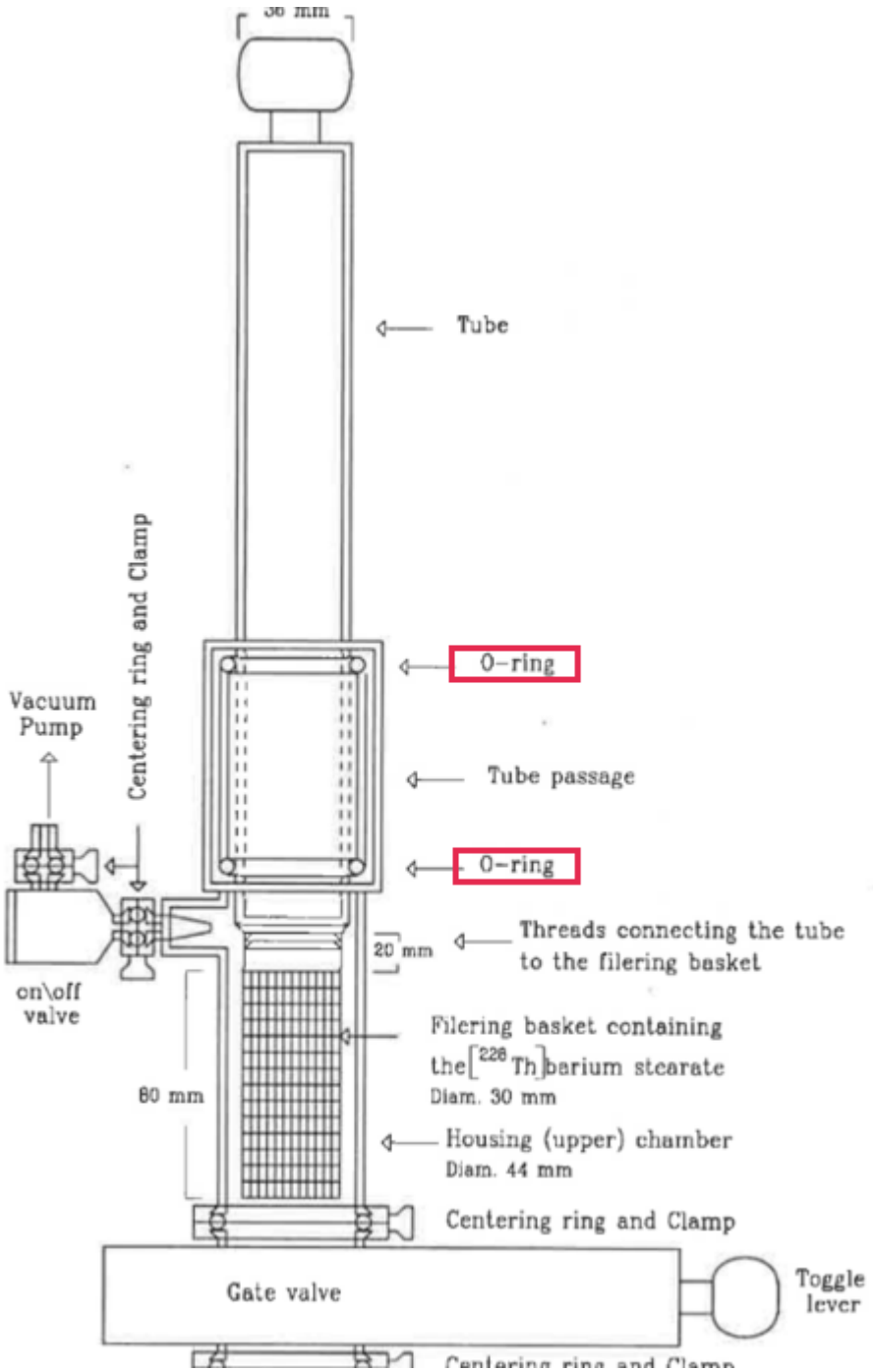
123. As explained above, this limitation is disclosed by Hassfjell-Hoff. *See* §IV(N) (claim 15).

124. The disclosure in the 603 patent of a rod including an O-ring matches the disclosure of Hassfjell-Hoff. *Compare* EX1001, Fig. 4 *with* EX1003, Fig. 2.



EX1001, Fig. 4.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642



EX1003, Fig. 2 (excerpt). This feature would have been obvious to a POSITA because Figure 2 of Hassfjell-Hoff already shows in detail that the O-ring is positioned so that it is touching the tube (*i.e.*, *rod*). Therefore, the Hassfjell-Hoff

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

rod "includes" and renders obvious at least one O-ring to form the gas tight seal with the tube in the closed position. This would have been obvious to a POSITA because Hassfjell-Hoff explicitly shows a configuration where the O-ring is touching the tube (*i.e.*, *rod*) to seal it.

H. Claim 16 "The system of claim 12, wherein the rod holds the precursor isotope source without having the precursor isotope source touch the interior surface."

125. As explained above, this limitation is disclosed by Hassfjell-Hoff. *See* §IV(O) (claim 16). Moreover, in my opinion, this claim would have been obvious to a POSITA because it is desirable to prevent the precursor isotope source from becoming deposited on the interior surface of the container, thereby preventing radiation contamination. EX1003, 6 (describing how the Rn gas fills the volume of the collection chamber and by this action decays and deposits the ^{212}Pb onto the walls of the container). Therefore, and as shown in Hassfjell-Hoff, it would have been obvious to a POSITA that to design the system such that the rod holds the precursor isotope source without having the precursor isotope source touch the interior surface. EX1003, Fig. 2. Doing so would have been within the skill and knowledge of a POSITA, would have led to predictable results, would have created a reasonable expectation of success, would have been compatible with Hassfjell-Hoff, and would have been a mere design choice. Such motivations would have been a matter of common sense and known to a POSITA.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

I. Claim 20 "The system of claim 12, wherein the precursor isotope source is configured to decay and emanate the one or more progeny isotopes into the container for 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours."

126. In my opinion, Hassfjell-Hoff renders this claim obvious. *See* §III(D)(4) (claim 20 construction); §V(E) (claim 10).

127. As I explain above, Hassfjell-Hoff discloses *the system of claim 12*. *See* §IV(K) (claim 12).

128. To the extent this claim is construed to mean at least (or more than) one of the listed times (*see* §III(D)(4) (claim 20 construction)), Hassfjell-Hoff explicitly discloses that "Filter membrane packets with [^{228}Th]barium stearate with ^{228}Th at the kBq level have shown unchanged emanation ability for ^{220}Rn during 1 yr….The generator has been operated with 40-50MBq (1.1-1.4mCi) of ^{228}Th for 1 yr, and the total amount of ^{212}Pb that can be collected inside the polyethylene bottle at saturation has decreased from 50 to 11% of the ^{228}Th radioactivity." EX1003, 7. A POSITA would recognize that this means that the generator was operated in a way "configured to decay and emanate the one or more progeny isotopes into the container" for at least 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours. A POSITA would have understood that the 10.6 hour half-life of ^{212}Pb would have meant that, after 10.6 hours of collection, the amount of ^{212}Pb would be about 50% the maximum expected to exist. Thus, allowing the system to emanate for 10.6 hours would have been obvious to try. A POSITA would have

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

understood that selection of the exact time was a matter of routine optimization. *See* §V(E) (claim 10); §VI(F) (claim 20); EX1007, Fig. 4, [0030].

VI. GROUND 3: CLAIMS 9-10, 18, 20 ARE OBVIOUS OVER HASSFJELL-HOFF AND O'HARA

A. Overview of Hassfjell-Hoff

129. My explanation of the Hassfjell-Hoff reference is above and incorporated here by reference into Ground 3. See §IV(A).

B. Overview of O'Hara

130. US Patent Application Publication No. 2018/0047474 to O'Hara was published on February 15, 2018 and entitled "System, Emanation Generator, and Process for Production of High-Purity Therapeutic Radioisotopes." EX1007, cover. I have been informed that O'Hara qualifies as prior art under 35 U.S.C. §102(a).

131. O'Hara was cited in the 603 patent in the International Search Report for PCT/EP2020/084701 dated February 17, 2021. However, the USPTO never rejected any claims of the 603 patent over O'Hara (or any other reference). EX1001, cover; EX1006. Therefore, it is my opinion that the Examiner erred by failing to consider O'Hara.

132. O'Hara discloses an isotope production system, emanation generator, and process for production of high-purity radioisotopes, such as ^{212}Pb and/or ^{212}Bi, suitable for therapeutic applications. EX1007, [0005]. The isotope production system, emanation generator, and processor of O'Hara address various problems in

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

prior art isotope production systems including high radiolytic degradation and breakthrough of high energy isotopes such as ^{224}Ra and ^{228}Th that can contaminate the recovered isotopes. EX1007, [0005].

133. O'Hara is analogous art to the 603 patent and was not considered during prosecution of the 603 patent. EX1001; EX1006.

134. In my opinion, O'Hara is analogous art to the 603 patent. O'Hara is from the same field of endeavor as the 603 patent. They are both patents in the field of radioisotope generators. EX1001; EX1007. In addition, Hassfjell-Hoff is reasonably relevant to the problem the patent is concerned with, as shown in my analysis below in Sections VI(C)-(F).

135. Based on my review of the prosecution history (EX1006), Hassfjell-Hoff appears to have not been considered during prosecution of the 603 patent.

C. Claim 9 "The method of claim 1, wherein allowing sufficient time for the at least one progeny isotopes to emanate into the container from the precursor isotope source comprises allowing sufficient time for the at least one progeny isotopes to emanate into the container from the precursor isotope source disposed in a sponge, a wool, a strip, or a sphere comprising at least one selected from the group consisting of: quartz, glass, mineral, paper, plastic, metal, ceramic, natural fibers, and synthetic fibers."

136. In my opinion, claim 9 is obvious by Hassfjell-Hoff in view of O'Hara.

137. As I explain above, Hassfjell-Hoff discloses *the method of claim 1*. *See* §IV(B) (claim 1).

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

1. Hassfjell Discussion

138. Hassfjell-Hoff discloses allowing sufficient time for the at least one progeny isotopes to emanate into the container from the precursor isotope source comprises allowing sufficient time for the at least one progeny isotope to emanate into the container from the filering basket, and that the filering basket has a capacity of 3-4 [^{228}Th]barium stearate packets. EX1003, 7. The [^{228}Th]barium stearate packets emanate gaseous ^{220}Rn which then decays into ^{212}Pb. EX1003, 7. However, Hassfjell-Hoff does not detail whether the filering basket and the [^{228}Th]barium stearate packets contained therein are a sponge, a wool, a strip, or a sphere comprising at least one selected from the group consisting of quartz, glass, mineral, paper, plastic, metal, ceramic, natural fibers, and synthetic fibers.

2. O'Hara Discussion

139. O'Hara discloses a radioisotope generator (§VI(B)) with a precursor isotope source disposed in a metal or mineral sponge. O'Hara discloses various examples of the precursor isotope source disposed on a mineral sorbent that is on a "permeable metal membrane, screen, or filter" or "porous disc." EX1007, [0020]-[0022]. In my opinion, a POSITA would have understood and found it obvious that the mineral sorbent, metal gas-permeable membrane, metal screen, metal filter, and mineral/metal porous disc are each a "sponge." As evidenced by Hassan and Lefebvre, gas-permeable membranes, screens, filters, and porous discs would have

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

been known in the art to have been formed of open-celled metallic foams. *See* EX1008, 2 (Table 1); EX1009, 2 ("metal sponge refers to highly porous materials with complex and interconnected porosity where the porosity cannot be subdivided into well defined cells"); EX1010. A POSITA would recognize that O'Hara's disclosure of mineral sorbent, gas-permeable membrane, screen, filter, and porous disc would have contained open pores (*i.e.*, a sponge) to allow gaseous ^{220}Rn to emanate from the ^{228}Th.

3. Motivation to Combine

140. In my opinion, a POSITA would have been motivated to combine Hassfjell-Hoff and O'Hara to implement the filter membrane packets and surrounding filering basket disclosed by Hassfjell-Hoff with the O'Hara gas permeable metal or mineral membrane, screen, filter, or porous disc (each are a sponge) containing the precursor isotope source. In my opinion, a POSITA would have understood that doing so would have been advantageous because the isotope-bearing membranes, screens, filters, and porous discs of O'Hara enable a greater quantity of the source isotope or a more dispersed source isotope to be assembled within a fixed diameter or geometry in the emanation generator to provide maximum emanation power for generating the emanation gas (*e.g.*, ^{220}Rn). EX1007, [0014]. This modification would have been within the skill and knowledge of a POSITA, would have led to predictable results, would have created

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

a reasonable expectation of success, would have been compatible with Hassfjell-Hoff, and would have been a mere design choice. Therefore, Hassfjell-Hoff in view of O'Hara renders claim 9 obvious.

D. Claim 10 "The method of claim 1, wherein allowing sufficient time for the precursor isotope source to decay comprises allowing 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours."

141. As I explained above, in my opinion, a POSITA would have understood in view of Hassfjell-Hoff alone that it would have been obvious for Hassfjell-Hoff's precursor isotope source configured to decay for at least 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours. *See* §V(E) (claim 10).

142. Moreover, in my opinion, Claim 10 is obvious by Hassfjell-Hoff in view of O'Hara. *See* §III(D)(3) (claim 10 construction).

143. O'Hara discloses a precursor isotope source configured to decay for at least 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours. Specifically, O'Hara discloses O'Hara discloses an analogous radioisotope generator. EX1007, [0015], [0018] (disclosing a "radon emanation generator" that contains installed Ra-224 that eventually decays and emanates Rn-220 and thereby forms Pb-212 and/or Bi-212). Similar to Hassfjell-Hoff, O'Hara discloses that the radioactive gas can be captured and collected by a collection device and retained

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

for a time sufficient to allow the decay of the radioactive gas to yield one or more high-purity daughter isotopes. EX1007, [0005].

144. In my opinion, a POSITA would have understood O'Hara to disclose that this amount of time can be various amounts. For example, figure 4 shows the results of tests of emanated gas when the emanation is performed for a time period of 0-3 days, or 0-72 hours. EX1007, Fig. 4, [0030]. Of those tests shown in figure 4, O'Hara performs tests at around 1 day (about 24 hours) and about 2.7 days (about 64 hours). EX1007, Fig. 4. O'Hara also discloses a separate example where the collection column was removed after about 2 days and the Pb-212 product isotopes resulting from Rn-220 decay were detected. EX1007, [0031]. O'Hara also fits a dotted line that estimates the emanated Rn count rate (counts per second, cps) as a function of the time. EX1007, Fig. 4. In my opinion, POSITA would have understood that this discloses that the claimed ranges of 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours would have been obvious to select based on the rising emanated count rate over time.

145. Based on O'Hara, in my opinion, a POSITA would have found it obvious to implement Hassfjell-Hoff to not only allow sufficient time for the precursor isotope source to decay, but also that the amount of time that the precursor isotope source is allowed to decay could be an amount of time of about 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours. This is

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

because O'Hara discloses that the decay of the radioactive gas to yield one or more high-purity daughter isotopes occurs over the amount of time claimed. EX1007, [0005]. In my opinion, a POSITA would have understood that, in the field of obtaining radioisotopes for therapeutics, this is beneficial because it provides a pure Pb-212 that is suitable for therapeutic use. EX1007, [0017]-[0018].

E. Claim 18 "The system of claim 12, wherein the precursor isotope source is disposed on a sponge, a wool, a strip, or a sphere comprising at least one material selected from the group consisting of: quartz, glass, mineral, paper, plastic, metal, ceramic, natural fibers, and synthetic fibers."

146. In my opinion, Claim 18 is obvious by Hassfjell-Hoff in view of O'Hara.

147. As I explain above, Hassfjell-Hoff discloses *the system of claim 12*. *See* §IV(K) (claim 12).

148. As explained above, in my opinion, a POSITA would have modified Hassfjell-Hoff in view of O'Hara such that the precursor isotope source is disposed on a sponge, a wool, a strip, or a sphere comprising at least one material selected from the group consisting of: quartz, glass, mineral, paper, plastic, metal, ceramic, natural fibers, and synthetic fibers. *See* §VI(C) (claim 9).

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

F. Claim 20 "The system of claim 12, wherein the precursor isotope source is configured to decay and emanate the one or more progeny isotopes into the container for 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours."

149. In my opinion, Claim 20 is obvious by Hassfjell-Hoff in view of O'Hara. *See* §III(D)(4) (claim 20 construction).

150. As I explain above, Hassfjell-Hoff discloses *the system of claim 12*. *See* §IV(K) (claim 12).

151. As explained above, in my opinion, a POSITA would have modified Hassfjell-Hoff in view of O'Hara to allow the precursor isotope source to decay and emanate the one or more progeny isotopes into the container for 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours. *See* §VI(D) (claim 10).

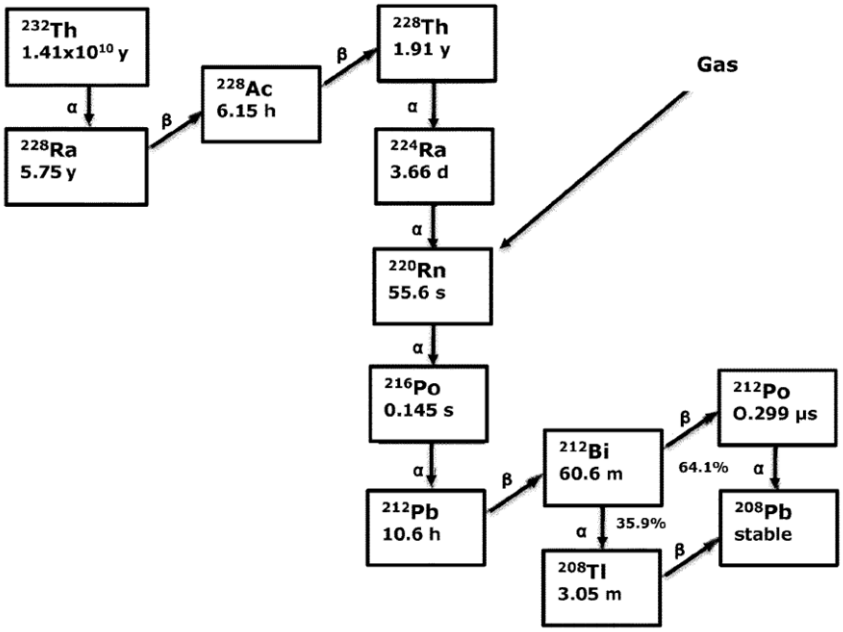
VII. GROUND 4: CLAIMS 1-3, 7-10, 12, 20 ARE UNPATENTABLE UNDER 35 U.S.C. §112

A. Claim 1 is non-enabled and lacks written description

152. Claim 1 recites "exposing an interior surface of a container to a precursor isotope source by sliding a rod…to an open position in which the precursor isotope source is exposed to the interior surface of the container, wherein the precursor isotope source is disposed on the rod; allowing sufficient time for the precursor isotope source to decay into ***one or more*** progeny isotopes and to emanate ***the one or more*** progeny isotopes into the container." EX1001, cl. 1. I have been asked whether there is enablement and written description support if claim 1 is interpreted to require sufficient time be allowed for the precursor isotope

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

source to decay into one or more progeny isotopes and **the same** one or more progeny isotopes to emanate into the container. In each embodiment of the 603 patent, only one progeny isotope (^{220}Rn) both decays from the precursor isotope source and emanates into the container. Only ^{220}Rn is in the gaseous state, therefore only ^{220}Rn can emanate. *See*, *e.g.*, EX1001, 18:25-27, 19:30-33, Fig. 1. In particular, figure 1 of the 603 patent denotes the gaseous state of ^{220}Rn as shown below:



EX1001, Fig. 1. Therefore, because it is impossible for there to be more than one progeny isotope that both decays from the precursor isotope source disclosed by the 603 patent and that also emanates into the container, in my opinion, the full scope of the claim lacks written description and is not enabled.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

B. Claim 2 is indefinite and non-enabled

153. Claim 2 recites "The method of claim 1, wherein exposing the interior surface to the precursor isotope source comprises exposing the interior surface to a thorium-228 isotope (^{228}Th) and/or a radium-224 isotope (^{224}Ra), the method further comprising allowing the ^{228}Th to decay into at least one of a radon-220 isotope (^{220}Rn) and a lead-212 isotope (^{212}Pb)." The wherein clause of claim 2 sets forth alternative precursor isotopes to which the interior surface is exposed. Specifically, three alternatives are effectively listed as possible: (i) ^{228}Th, (ii) ^{224}Ra, and (iii) a combination of ^{228}Th and ^{224}Ra. However, of these possibilities, (i) is not possible, because the radioactive decay of ^{228}Th into ^{224}Ra cannot be stopped or even slowed down, and therefore any ^{228}Th source must include some portion of ^{224}Ra as would be apparent to a POSITA. Therefore, in my opinion, the full scope of Claim 2 is not enabled and is indefinite.

154. Moreover, the "further comprising" portion of claim 2 renders the claim indefinite because under alternative (ii) there is no ^{228}Th. Therefore, in my opinion, it is not reasonably certain to a POSITA whether this claim requires allowing the (nonexistent) ^{228}Th to decay. Under alternative (ii), if the claim does require allowing ^{228}Th to decay, then it is not enabled.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

C. Claim 3 is indefinite and non-enabled

155. Claim 3 recites "The method of claim 2, the method further comprising allowing the ^{212}Pb to deposit on the interior surface of the container." However, in claim 2 the ^{228}Th is allowed to decay into (i) ^{220}Rn, (ii) ^{212}Pb, or (iii) a combination of ^{220}Rn and ^{212}Pb.

156. The literal scope of this claim covers allowing the ^{228}Th to decay into ^{220}Rn only, which is not possible. Moreover, even if it were possible (it is not), then no ^{212}Pb is present to be deposited on the interior surface of a container. As such, in my opinion, claim 3 is indefinite and non-enabled for similar reasons as claim 2.

D. The language of Claim 7 is non-sensical, therefore indefinite

157. Claim 7 recites "The method of claim 1, wherein exposing the interior surface of the container to the precursor isotope source exposing the interior surface of the container to the precursor isotope source without having the precursor isotope source touch the interior surface." As shown by the yellow and green highlighting, claim 7 repeats language requiring *exposing*, which is non-sensical.

158. It is my understanding that there are many possible ways to fix this claim, but I am not sure which one would have been chosen by the Patent Owner. Some possible ways to rewrite the claim to fix it include:

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

- adding "comprising" as I discuss in §III(D)(2);
- adding "consisting" instead of "comprising"; or
- deleting the repeated phrase and adding the words "further comprising"

159. In my opinion, a POSITA would not have known which correction is covered by the claim as written, and therefore this claim is indefinite.

E. Claims 8 and 9 are indefinite for lack of antecedent basis

160. Each of claims 8 and 9 recites "allowing sufficient time for ***the at least one progeny isotopes*** to emanate into the container." Claim 1, from which each of claims 8 and 9 depend, does not recite "at least one progeny isotopes." In addition, in my opinion, a POSITA would not be aware of the meaning of such term in the context of either claim because it would not be apparent which progeny isotopes would be allowed to emanate into the container as opposed to the one or more progeny isotopes that are emanated as disclosed in claim 1.

F. Claim 10 is indefinite and lack written description

161. To the extent that claim 10 is construed to require exactly one of the listed times, in my opinion, there is no written description support regarding how a POSITA would perform the method for exactly the listed times. Claim 10 is indefinite because, in my opinion, a POSITA would not know whether "allowing" refers to the time the source decays or the time the bottle is left in the apparatus.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

G. Claim 12 is non-enabled and lacks written description

162. For the same reasons as claim 1, in my opinion, claim 12 is non-enabled and lacks written description. §VII(A).

H. Claim 20 is indefinite, lacks written description, and is non-enabled

163. To the extent that claim 20 is construed to require exactly one of the listed times, in my opinion, there is no written description support or enabling disclosure regarding how a POSITA would configure the precursor isotope source to decay and emanate the one or more progeny isotopes into a container for an exact time (*e.g.*, 10 hours). It is impossible to "configure" a precursor isotype source to decay for an exact amount of time, because unstable precursor isotopes will continue to decay emitting ionizing radiation for as long as a portion of the precursor isotope source is made up of unstable isotopes. Radioactive decay continues regardless of any action taken by a user (there will always be some amount of radioisotope emitting radiation too faint to detect). Therefore claim 20 is not enabled. Moreover, in my opinion, claim 20 is indefinite because a POSITA would not know whether the claim requires cessation of decay at an exact time.

VIII. SECONDARY CONSIDERATIONS

164. I am not aware of any relevant information related to secondary considerations of obviousness. For example, I am not aware of any attempt to

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

commercialize the claimed technology in a product or through licensing. To the extent Patent Owner comes forward with any such information, I will consider it.

IX. AVAILABILITY FOR CROSS-EXAMINATION

165. In signing this Declaration, I recognize that the Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during a time as mutually agreed between the parties.

X. RIGHT TO SUPPLEMENT

166. I reserve the right to supplement my opinions in the future to respond to any arguments that the Patent Owner raises. This Declaration represents only those opinions that I have formed to date. I reserve the right to revise, supplement, and/or amend my opinions stated herein based on new information that becomes available to me and on my continuing analysis of the materials already provided.

XI. CONCLUSION

167. I may utilize the documents cited and/or listed herein, or portions of those documents, as exhibits at any hearing or trial in this proceeding. I may further prepare and use exhibits that summarize portions of my testimony or key

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

terms or concepts presented therein, or other demonstrative exhibits, at any hearing or trial in this proceeding.

168. I reserve the right to supplement my testimony and this report in response to any judicial determinations, in response to the arguments expressed by the Patent Owner or the opinions of the Patent Owner's experts in this proceeding, and/or in light of additional evidence or testimony brought forth at trial or otherwise brought to my attention after the date of my signature on the cover page.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

APPENDIX 1

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Biographical Sketch

Saed Mirzadeh

1039 Governor Dempsey Dr.,
Santa Fe, NM 87501-1045
email: saedmirzadeh@gmail.com,
cell phone: 865-599-6613

Education/Training:

National University of Iran, Tehran, Iran	B.S.	1969	Chemistry
University of New Mexico, Albuquerque, NM	Ph.D.	1979	Radiochemistry
Brookhaven National Laboratory, L.I., NY	Postdoc	1980	Nuclear Chemistry

Research and Professional Experience:

2021-present Consultant, Rdiomedix Inc., 9701 Richmond Avenue, Suite 222, Houston, TX 77042
Consultant, Cardinal Health, 7200 Cardinal Pl., Dublin, OH 43017.

1989-2020 Distinguished Staff Scientist and ORNL Corporate fellow (retired 9/31/2020), Nuclear and Radiochemistry Group, Nuclear Security & Isotope Technology Division, Oak Ridge National Laboratory. *Research in radioisotope production, cross section measurements, neutron-induced reactions model calculations, mentor for MS and Ph.D. graduate students*

1993-1993 Visiting Scientist, Australian Nuclear Science and Technology. *Research on reactor production of medical radioisotopes*

1987-1989 Scientist, Radiation Oncology, National Cancer Institute, National Institutes of Health. *Research on radiometal labeling of antibodies.*

1985-1987 Adjunct Associate Professor of Chemistry, Natural Sciences Division, Long Island University. *Taught courses on Instrumental Analysis with an emphasis on neutron activation analysis*

1981-1987 Scientist, Medical Department, Brookhaven National Laboratory. *Research in radioisotope production, cross section measurements, charged particle-induced reactions*

1980-1981 Research Associate, Chemistry Department, Brookhaven National Laboratory. *Experimental Nuclear chemistry, synthesis of short-lived radionuclide far from stability.*

1979 Research Associate, Medical Radioisotope Program, Los Alamos National Laboratory. *Research on medical radioisotope production*

Selected Publications:

A. C. Peacock, R. Copping, J. R. Griswold, R. A. Boll, D. L. Denton, J. A. Gaugler, Widner, K. E. Murphy, D. Stracener. and S. Mirzadeh, "Separation of Radium from Barium and other Group II Elements Using Reverse Phase Cation Exchange Chromatography in Citrate Media" for submission to Radiochimica Acta (2024) (under DOE/ORNL internal review).

J. G. Mwakisege, G. Schweitzer and S. Mirzadeh, "Synthesis and Stability of Actinium-225 Endohedral Fullerenes, $^{225}Ac@C_{60}$", ACS Omega 5(42):27016-27025, October 2020, DOI:10.1021/acsomega.0c01659.

AdvanCell
Ex. 1002 - Page 87

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Selected Publications (cont.):

J. G. Mwakisege, G. Schweitzer and S. Mirzadeh, "Synthesis and Stability of Actinium-225 Endohedral Fullerenes, $^{225}Ac@C_{60}$", ACS Omega 5(42):27016-27025, October 2020, DOI:10.1021/acsomega.0c01659.

S. Mirzadeh, "Innovation, Impact and Strategic Importance of Alpha Emitting Radionuclides", Journal of Medical Imaging and Radiation Sciences, **50**, S6-S10 (2019).

J. R. Griswold, C. U. Jost, D. W. Stracener, S. H. Bruffey, D. Denton, M. Garland, L. Heilbronn, and S. Mirzadeh, "Production of ^{229}Th for Medical Applications: Excitation Functions of Low-Energy Protons on ^{232}Th Targets", Physical Review C, **98**, 044607 (2018).

J. R. Griswold, D. G. Medvedev, J. W. Engle, R. Copping, J. M. Fitzsimmons, V. Radchenko, J. C. Cooley, M. E. Fassbender, D. L. Denton, K. E. Murphy, A. C. Owens, E. R. Birnbaum, K. D. John, F. M. Nortier, D. W. Stracener, L. H. Heilbronn, L. F. Mausner, S. Mirzadeh, "Large Scale Accelerator Production of ^{225}Ac: Effective Cross Sections for 78-192 MeV Protons Incident on ^{232}Th Targets", Applied Radiation and Isotopes, 118, 366-374, 2016.

S. Hogle, R. A. Boll, K. Murphy, D. Denton, A. Owens, T. J. Haverlock, M. Garland, and S. Mirzadeh, "Reactor Production of Thorium-229", Applied Radiation and Isotopes, 114, 19-27, 2016.

S. Mirzadeh, Accelerator Produced ^{225}Ac via proton Spallation of ^{232}Th: a joint research program among ORNL, LANL, and BNL, ORNL/TM-2014/142 (2014).

S. Mirzadeh, L.F., Mausner, and M.A. Garland, "Reactor-Produced Medical Radionuclides. In Handbook of Nuclear Chemistry, Second Edition (Volume 4, Radiochemistry and Radiopharmaceutical Chemistry in Life Sciences, Chapter 38, PP 1857 – 1902)", Vertes, A, Nagy, S, Klencsar, Z, Lovas, RG, Roesch, F., editors. New York, NY: Springer (2011)

M. D. Diener, J. M. Alford, S. J. Kennel, and S. Mirzadeh, "$^{212}Pb@C_{60}$ and its Water-Soluble Derivatives: Synthesis, Stability and Suitability for Radioimmunotherapy", J. Am. Chem. Soc., 129, 5131, 2007.

Mirzadeh, S., "Generator-produced Alpha-emitters", Proceedings of CIRMS Medical Subcommittee Workshop on Radionuclides Used in Bone Pain Palliation Therapy NIST, Washington D.C., September 27, 1996, *Applied Radiation and Isotopes*, **49**, 345-349 (1998).

R. A. Boll, S. Mirzadeh, and S. J. Kennel, "Optimization of Radiolabeling of Immunoproteins with ^{213}Bi, Radiochimica Acta **79**, 145-149, (1997).

S. Mirzadeh, K. Kumar and O. A. Gansow, "The Chemical Fate of ^{212}Bi-DOTA Formed by ß-Decay of $^{212}Pb(DOTA)^{2-}$ Complex", *Radiochimica Acta*, 60,1-10 (1993).

S. Mirzadeh, M. W. Brechbiel, and O. A. Gansow, "Radiometal Labeling of Immunoproteins: Covalent Linkage of 2-(4-isothiocyanatobenzyl)-DTPA to Immunoglobulin", *Bioconjugate Chemistry* **1**, 59-65 (1990).

AdvanCell
Ex. 1002 - Page 88

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Selected Patents:

Mirzadeh, S. and R. M. Lambrecht, "*Methods for the Simultaneous Preparation of Radon-211 and Xe-125, Astatine-211, Iodine-125 and Iodine-123*", U.S. Patent No. 4,644,869, May 12, 1987.

Mirzadeh, S. and R. M. Lambrecht, "*Process for Producing Astatine-211 for Radiopharmaceutical Use*", U.S. Patent No. 4,681,727, July 21, 1987.

Mirzadeh, S., R. E. Whipple, P. M. Grant, H. A. O'Brien, Jr., "*Evaporation-Based Ge/Ga(68) Separation*", U.S. Patent No. 4,268,730, February 3, 1981.

Synergistic Activities:

Organizer of symposiums:

"International Symposium on Targeted Alpha Therapy", June 2013, ORNL

"Radiometals in Therapy and Diagnosis" under auspices of Divisions of Nuclear Chemistry and Technology & Inorganic Chemistry, American Chemical Society National Meeting, Dallas, TX, March 29, 1998.

"Radiochemistry and Radioimmunotherapy", under auspices of Division of Nuclear Chemistry and Technology, American Chemical Society National Meeting, Orlando, Fl, August 25-29, 1996.

"Radionuclide Generators for Nuclear Medicine Applications," under auspices of Division of Nuclear Chemistry and Technology, American Chemical Society National Meeting, Washington, D.C., August 23-28, 1992.

Committee Member:

Nuclear Science Advisory Committee (NSAC), Isotopes Subcommittee (2015), The editorial board of the Journal of Applied Radiation and Isotopes (2000-2015). American Chemical Society Divisions of Nuclear Chemistry and Technology (DNCT) and Physical Chemistry, (1979-2010). Review committees for DOE, NIH, and Government of Norway Grant Proposals.

Editorial. Editor of Journal Applied Radiation and Isotopes, 2010 to 2015.

Thesis Advisor and Postgraduate-Scholar Sponsor (Total: 6 Postdoctoral, 8 PhDs; >14 MSc)

Postdoctoral Fellows: Rose Boll, ORNL; Nan Chen, Provision; Ekaterina Dadachova, Univ. of Saskatchewan; Justin Griswold, ORNL; Susan Hogle, ORNL; Jon Woodward, Y-12

PhD Students: Rose Boll, ORNL; Marc Garland, DOE; Justin Griswold, ORNL; Zac Kulage, Pantex; Mark Mclaughlin, Univ. of Nebraska Medical; Jessika Rojas, VCU; Miguel Toro-Gonzalez, VCU, Onur Alp Ersöz, Ege University, Turkey.

MSc Students: Jane Wallen, UT, Chelsea Burnham, NuScale Power; D. W. Cagle, FBI; Tyler Cantrell, Cardinal Health; A. M. Craig, UCSD; Justin Griswold, ORNL; James Hinderer, Siemens Medical; Hal Lovett, US Army; Rita Lusk, Norfolk Naval Shipyard; Dairin Malkemus, Univ. of Tennessee; Dan Marsh, Canberra; Jofa Mwakisege, US Army; Phillip Walsh, LSU; Spencer Walsh, Nuclear Fuel Services, and others

AdvanCell
Ex. 1002 - Page 89

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

PUBLICATIONS

Book chapters, reviews, monographs, and proceedings

S. Mirzadeh, Accelerator Produced ^{225}Ac via proton Spallation of ^{232}Th: a joint research program among ORNL, LANL, and BNL, ORNL/TM-2014/142 (2014)

CU Jost, JR Griswold, SH Bruffey, DW Stracener, CL Williams, and S Mirzadeh, "Measurement of cross sections for the ^{232}Th[p,4n]^{229}Pa reaction at low proton energies". In proceedings of 22nd International Conference on the Application of Accelerators in Research and Industry, August 5 – 10, 2012, Fort Worth, Texas, USA.

B. J. Egle, S. Mirzadeh, B. A. Tatum, V. K.Varma, E. C. Bradley, T. W. Burgess, W. S. Aaron, J. L. Binder, J. R. Beene, M. Saltmarsh, "A Cyclotron Concept To Support Isotope Production for Science and Medical Applications", Proceedings of the American Nuclear Society Topical Meeting; Accelerator Applications, Knoxville, TN, April, 2011.

F.F. KNAPP, Jr., S. MIRZADEH, M Garland, B. Ponsard, R. Kuznetsov, 2010, REACTOR PRODUCTION AND PROCESSING OF ^{188}W (Chapter 5). In Production of Long Lived, Parent Radionuclides, for Generators: ^{68}Ge, ^{82}Sr, ^{90}Sr and ^{188}W, IAEA RADIOISOTOPES AND RADIOPHARMACEUTICALS SERIES No. 2.

Mirzadeh, S, Mausner, LF, Garland, MA. "Reactor-Produced Medical Radionuclides. In Handbook of Nuclear Chemistry, Second Edition (Volume 4, Radiochemistry and Radiopharmaceutical Chemistry in Life Sciences, Chapter 38, PP 1857 – 1902)", Vertes, A, Nagy, S, Klencsar, Z, Lovas, RG, Roesch, F. , editors. New York, NY: Springer (2011).

Garland, MA, Mirzadeh, S, Schenter, RE. 2008. Development of ANS Standard 19.12 Nuclear Data for Isotope Production Calculations for Medical and Other Applications. Trans. American Nuclear Society 98:912.

Lovett, HA, Knight, TW, Garland, MA, Mirzadeh, S. 2007. Evaluation of Tellurium-125 Metastable Production Pathways. Trans. American Nuclear Society 96:363.

Knapp, F. F., Jr., Mirzadeh, S. and Garland, M. "The Availability of Lutetium-177 from Research Reactors, " pp. 100-109. *Report*, of the 2nd Research Coordination Meeting on the Development of Generator Technologies for Therapeutic Radionuclides, April 3-7, 2006, European Institute of Oncology, Milan, Italy; IAEA, Vienna, Austria.

Knapp, F. F.,Jr., Mirzadeh, S., Garland, M. and Ponsard, B. "Reactor Production of Tungsten-188," *Invited, for*, IAEA Special Publication, *in preparation*, 2006.

Knapp, F. F., Jr., Mirzaeh, S., and Garland, M. "The Continuing Important Role of High Flux Reactors for Production of Therapeutic Medical Radioisotopes," *Invited Lecture, For, TECDOC, International Symposium on Trends in Radiopharmaceuticals*, IAEA, Vienna, Austria, *in press,* 2006.

AdvanCell
Ex. 1002 - Page 90

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Book chapters, monographs, and proceedings (cont.)

Boll, R. A., Garland, G., and Mirzadeh, S., "Reactor Production of Thorium-229", Proceedings of the International Conference on Nuclear Data for Science and Technology, Santa Fe, New Mexico, USA, Sept 26, 2004, American Institute of Physics, AIP Conference Proceedings, Haight et al. Editor, Vol. **769**, pp1674-1675 (2005).

Mirzadeh, S., Mausner, L. F., and Garland, M., "Reactor-Produced Medical Radioisotopes@, in Handbook of Nuclear and Radiochemistry", A. Vertes, S. Nagy and Z. Klencsar, *Editors*; Kluwer Publishers. Vol. **4**, pp 1-46 (2003).

Mausner, L. F., and Mirzadeh, S., "Reactor Production of Radionuclides in Handbook of Radiopharmaceuticals: Radiochemistry and Applications", M.J. Welch and C. S. Redvanly Editors, John Wiely and Sons Ltd, West Sussex, England, Chapter 3, pp 87-118 (2003).

Du, M., Peretz, F., Boll, R. A., Mirzadeh, S., "Purification of Thorium-229 for Medical Applications", Proceedings of Symposium on Radioanalytical Methods in Interdisciplinary Research, 233rd American Chemical Society National meeting, Orlando, FL, April 10, 2002. ACS Symposium No. 868, C. A. Laue and K. L. Nash Editors, American Chemical Society, WDC, pp 193-203, (2003).

Ponsard, B., Hiltunen, J., Vera-Ruiz, H., Beets, A. L., Mirzadeh, S. and Knapp, F. F., Jr. "The Tungsten-188/Rhenium-188 Generator: Effective Coordination of Tungsten-188 Production Between the HFIR and BR2 Reactors," *J. Radioanalyt. Nucl. Chem.,* 257, 169-174 (2003).

Knapp, F. F., Jr., Mirzadeh, S., Beets, A. L. and Du, M. "Production of Therapeutic Radioisotopes in the ORNL High Flux Isotope Reactor," *In, Proceedings*, International Isotope Society Meeting, Boston, MA, June 2-6, 2003.

Mirzadeh, S., Du, M. Beets, B., Knapp, Jr. F. F. "Thermo-separation of Neutron Irradiated Tungsten from Re and Os", Proceedings of Nuclear Separations for Radiopharmacy, American Chem. Society, National Meeting, Boston, MA, Aug. 1998, Industrial *and Engineering Chemistry Research*, **39**, 3169-3172 (2000).

Knapp, F. F., Beets, A. L., Mirzadeh, S., Alexander, C. W., and Hobbs, R. L. "Production of Medical Radioisotopes in the ORNL HFIR for Cancer Therapy", Proceedings of the 13th Radiochemical Conference, Marianzke Lazne, Czech Republic, April 19-24, 1998.

Mirzadeh, S., "Generator-produced Alpha-emitters", Proceedings of CIRMS Medical Subcommittee Workshop on Radionuclides Used in Bone Pain Palliation Therapy NIST, Washington D.C., September 27, 1996, *Applied Radiation and Isotopes*, **49**, 345-349 (1998).

Knapp, F. F., Jr., Mirzadeh, S., Beets, A. L., et al., "Reactor-Produced Radioisotopes from ORNL for Bone Pain Palliation", Proceedings of CIRMS Medical Subcommittee Workshop on Radionuclides Used in Bone Pain Palliation Therapy NIST, Washington D. C., September 27, 1996, *Applied Radiation and Isotopes*, **49**, 309-315 (1998).

Boll, R. A., Mirzadeh, S. and Kennel, S. J., "Optimization of Radiolabeling of Immunoproteins with ^{213}Bi", Proceedings of Symposium on Radiochemistry and Radioimmunotherapy, 212th ACS National Meeting, Orlando, Fl, Aug. 24-28, 1996, *Radiochimica Acta*, **79**, 145-149 (1997).

AdvanCell
Ex. 1002 - Page 91

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Book chapters, monographs, and proceedings (cont.)

Kennel, S. J. and Mirzadeh, S., "Vascular Targeting for Radioimmunotherapy with ^{213}Bi". Proceedings of Symposium on Radiochemistry and Radioimmunotherapy, 212th ACS National Meeting, Orlando, Fl, Aug. 24-28, 1996, *Radiochimica Acta,* **79**, 87-91 (1997).

Boll, R. A., Mirzadeh, S., Kennel, S. J., DePaoli, D. W., and Webb, O. F., "Bi-213 for Alpha-particle-mediated Radioimmunotherapy", Proceedings of XII International Symposium on Radio-pharmaceutical Chemistry, Uppsala, Sweden, June 15-19, 1997, *Journal of Labelled Compounds*, **XL**, 341-343 (1997).

Dadachova, E., Izard, M., and Mirzadeh, S., "Automated Production of Carrier-free Radiolanthanides", Proceedings of XII International Symposium on Radiopharmaceutical Chemistry, Uppsala, Sweden, June 15-19, 1997, *Journal of Labelled Compounds*, **XL**, 254-256 (1997).

Packard, A. B., Spaeth, K., Kronauge, J. F., and Mirzadeh, S., "Platinum-195m Radiopharmaceuticals for Therapy", Proceedings of XII International Symposium on Radiopharmaceutical Chemistry, Uppsala, Sweden, June 15-19, 1997, *Journal of Labelled Compounds*, **XL**, 354-356 (1997).

Mirzadeh, S. and Packard, A. B. (1995), "Synthesis of AZT-Pt(terpy) -- A potential compound for radiotherapy of AIDS", Proceedings of symposium on Advances in Bioconjugate Chemistry, 210th ACS National Meeting, Chicago, Ill, Aug. 20-24, 1995.

Mirzadeh, S. and Knapp, F. F. Jr., "Biomedical Generator Systems", *Journal of Radioanalytical and Nuclear Chemistry - Articles*, **203**, 469-486 (1996).

Mirzadeh, S. and R. M. Lambrecht, "Radiochemistry of Germanium", *Journal of Radioanalytical and Nuclear Chemistry - Articles*, **202**, 7-102 (1996).

Knapp, F. F., Jr. and Mirzadeh, S., "Radionuclide Production, Section 1. Reactors", in *Principles of Nuclear Medicine* (H. N. Wagner, Z. Szabo and J. W. Buchanan, editors), W. B. Sanders, Co., New York, (1995), pp 135-144, ISBN 0-7216-9091-2.

Mahmood, S. T., Mirzadeh, S., Pace, J. V., III, Farrel, K. and Oliver, B. M., *Neutron Dosimetry of the HFIR Hydraulic Tube Facilities*, **ORNL/TM 12831** (1994).

Mirzadeh, S., Alexander, C. W., McManamy, T. and Knapp, F. F., *Projected Medical Radioisotope Production Capabilities of the Advanced Neutron Source (ANS)*, **ORNL/TM-12010S** (1994).

Knapp, Jr., F. F., Mirzadeh, S., Beets, A. L., Sharkey, R., Griffiths, G., and Goldenberg, D. M. "Curie-Scale Tungsten-188/Rhenium-188 Generators Can Cost-Effectively Provide Carrier-Free Rhenium-188 for Routine Clinical Applications," Fourth International Symposium on Technetium and Rhenium in Chemistry and Nuclear Medicine, Bressanone, Italy, September 12-14, 1994, *in press.*

Knapp, Jr., F. F., and Mirzadeh, S. "The Continuing Important Role of Radionuclide Generator Systems for Nuclear Medicine," *Invited Review Article*, European. Journal of Nuclear Medicine, **20**, 1152-1165 (1194).

AdvanCell
Ex. 1002 - Page 92

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Book chapters, monographs, and proceedings (cont.)

Dadachova, E., Mirzadeh, S., Lambrecht, R. M., Hetherington, E. and Knapp, F. F., "Separation of Carrier-free ^{166}Ho from ^{166}Dy in a Biomedical Generator System", in *Synthesis and Applications of Isotopically Labelled Compounds*, John Wiley and Sons Ltd. (1995), pp 229-231.

Dadachova, E., Mirzadeh, S. and Lambrecht, R. M., "Alumina-based ^{188}W6^{188}Re Biomedical Generator -- Physical and Chemical Study of Tungstate Ion Adsorption on Al_2O3, in *Synthesis and Applications of Isotopically Labelled Compounds*, John Wiley and Sons Ltd. (1995), pp 231-236.

Kamioki, H., Mirzadeh, S., and Lambrecht, "Pre-clinical evaluation of ^{188}W6^{188}Re Biomedical Generator", 10th International Symposium on Radiopharmaceutical Chemistry, Kyoto, Japan, October 25-28 (1993).

Mirzadeh, S., Di Bartolo, N., Smith, S. V., Lambrecht, R. M., Knapp, F. F. Jr., "^{166}Dysprosium-^{166}Holmium *In Vivo* Generator", 10th International Symposium on Radiopharmaceutical Chemistry, Kyoto, Japan, October 25-28 (1993).

Mirzadeh, S., Hetherington, E. and Knapp, F. F., and Lambrecht, R. M., "Carrier-free Holmium-166 from ^{166}Dy/^{166}Ho Biomedical Generator System, 10th International Symposium on Radiopharmaceutical Chemistry, Kyoto, Japan, October 25-28 (1993).

Mirzadeh, S., "Advances in the ^{188}W-^{188}Re Generator", in *Proceedings of the International Symposium on Advances in Radiopharmaceuticals*, Sydney, Australia, February 5, 1993.

Mirzadeh, S., R. E. Schenter, A. P. Callahan and F. F. Knapp, *Production Capabilities in U. S. Nuclear Reactors for Medical Radioisotopes*, **ORNL/TM-12010** (1992).

Mirzadeh, S., D. E. Rice, A. P. Callahan and F. F. Knapp, Jr., "The ^{194}Os/^{194}Ir Generator -- Production and Purification of ^{194}Os", in *Proceedings of the IX International Symposium on Radiopharmaceutical Chemistry*, Paris, France, April 6-10 (1992), pp 471-473.

Brechbiel, M. W., C. G. Pippin, S. Mirzadeh, C. Wu, T. J. McMurry, O. A. Gansow, D. Colcher, D. E. Milenic, M. Roseli, R. Huneke and M. Strand, "Synthesis of 2-(p-SCN-benzyl)- trans-cyclohexyl-DTPA for α-particle Mediated Radioimmunotherapy", in *Proceedings of the IX International Symposium on Radiopharmaceutical Chemistry*, Paris, France, April 6-10 (1992), pp375-378.

Knapp, F. F. Jr., E. C. Lisic, S. Mirzadeh, A. P. Callahan, and D. E. Rice, "A New Clinical Prototype Tungsten-188/Rhenium-188 Generator to Provide High Levels of Carrier-free Rhenium-188 for Radioimmunotherapy (RIT)", in *Proceedings of the European Association of Nuclear Medicine Meeting*, Vienna, Austria, September 1-5, 1991; Nuclear Medicine in Research and Practice, Schattauer Verlag, Stuttgart, pp 183-186 (1992).

Mirzadeh, S. and Y. Y., Chu "Production of Ga-66, A Positron Emitter for Radioimmunotherapy", in *Proceedings of the International Conference on Nuclear Data for Science and Technology*, Julich, Germany, May 1991, S. M. Qaim Editor, (ISBN 0-387-55100X), Springer Verlag, New York (1992) pp 619-621.

AdvanCell
Ex. 1002 - Page 93

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Book chapters, monographs, and proceedings (cont.)

Mirzadeh, S., F. F. Knapp, Jr. and A. P. Callahan, "Production of Tungsten-188 and Osmium-194 in a Nuclear Reactor for New Clinical Generators". In *Proceedings of the International Conference on Nuclear Data for Science and Technology*, Julich, Germany, May 1991, S. M. Qaim Editor, (ISBN 0-387-55100X), Springer Verlag, New York (1992) 595-597.

Knapp, F. F. Jr., A. P. Callahan, S. Mirzadeh, C. Brihaye and M. Guillaume, "The Development of New Radionuclide Generator Systems for Nuclear Medicine Applications", in *Progress in Radiopharmacy* (P. A. Schubiger and G. Westera eds.), Development in Nuclear Medicine Series, Vol. 22 (ISBN 0-387-55100-x), Kluwer Academic Publishers (1992) pp 67-88.

Gansow, O. A., M. W. Brechbiel, S. Mirzadeh, D. Colcher and M. Roselli, "Chelates and Antibodies: Current Methods and New Directions". In *Cancer Imaging with Radiolabeled Antibodies*, D. M. Goldenberg editor, Kluwer Academic Publishers (1990) pp 153-171.

Pippin, C. G., S. Mirzadeh, and O. A. Gansow, "Kinetics of the Isotope Exchange Between Copper(II) and Copper(II)-1,4,7-Triazacyclonane-N,N',N" Triacetate". In *Proceedings of the 5th International Symposium on Radiopharmaceutical Chemistry*, Princeton, New Jersey, June 1990, Journal of Labeled Compounds and Radiopharmaceuticals, **29** (suppl.), 227-229 (1990).

Clem, R., R. M. Lambrecht, S. Mirzadeh, C. G. Pippin, M. W. Brechbiel, M. Roselli, O. A. Gansow, and D. Colcher, "Radiochemistry of Lead-203 for Radiolabeling Antibody Conjugates". *Proceedings of the 5th International Symposium on Radiopharmaceutical Chemistry*, Princeton, New Jersey, June 1990, Journal of Labeled Compounds and Radiopharmaceuticals, **29** (suppl.), 335-337 (1990).

Mirzadeh, S. and R. M. Lambrecht, "Measurement of the Cyclotron Beam Energy of the Alpha Particle by Rutherford Scattering in Gold Foil". In *Proceedings of the IAEA Consultants' meeting on Data Requirements for Medical Radioisotope Production*, K. Okamato Editor, IAEA INDC(NDC)-195/GZ January 1988.

Mausner, L. F., R. Mahr, J.A. Vachiere S. C. Srivastava and S. Mirzadeh, "Production of High Specific Activity Sn-117m the Szilard-Chalmers Process". In *Proceedings of the 7th International Symposium on Radiopharmaceutical Chemistry, Groningen, the Netherlands*, July 1988, Journal of Labeled Compounds and Radiopharmaceuticals, **26** (suppl.), 177-178 (1988).

Gansow, O. A., M. W. Brechbiel, S. Mirzadeh, M. Roselli, D. Colcher, A. Raubitschek and J. Schlom. "Difference in the Biodistribution of Indium and Yttrium Labeled Monoclonal Antibodies". In *Proceedings of the 7th International Symposium on Radiopharmaceutical Chemistry, Groningen, the Netherlands*, July 1988, Journal of Labeled Compounds and Radiopharmaceuticals, **26** (suppl.), 290-292 (1988).

Mausner, L. F., S. Mirzadeh, and S. C. Srivastava, "A New Spallation Radionuclide Research and Production Facility". In *Proceedings of the 6th International Symposium on Radiopharmaceutical Chemistry*, Boston, Massachusetts, June 1986, Journal of Labeled Compounds and Radiopharmaceuticals, **18** (suppl.), 1280-1283 (1986).

AdvanCell
Ex. 1002 - Page 94

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Book chapters, monographs, and proceedings (cont.)

Mirzadeh, S., L. F. Mausner, and S. C. Srivastava, "Design of a Fully Automated, In-Beam, Continuous-Flow I-123 Production System". In *Proceedings of the 6th International Symposium on Radiopharmaceutical Chemistry*, Boston, Massachusetts, June 1986, Journal of Labeled Compounds and Radiopharmaceuticals, **18** (suppl.), 1386-1388 (1986).

Mausner, L. F., S. Mirzadeh, T. Prach, and P. Richards, "Production and Separation of Tin-117m for Bone Radiotherapy". In *Proceedings of the 5th International Symposium on Radiopharmaceutical Chemistry,* Tokyo, Japan, July 1984, Journal of Labeled Compounds and Radiopharmaceuticals, **11** (suppl.), 1284-1285 (1984).

Mirzadeh, S., M. Kahn, P. Grant, and H. A. O'Brien, Jr., "A Distillation-based Ge(68)-Ga(68) Positron Generator". In *Proceedings of the Second International Congress of the World Federation of Nuclear Medicine and Biology*, Washington, D.C., 1978.

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Publications in referred journals

A. C. Peacock, R. Copping, J. R. Griswold, R. A. Boll, D. L. Denton, J. A. Gaugler, Widner, K. E. Murphy, D. Stracener. and S. Mirzadeh, "Separation of Radium from Barium and other Group II Elements Using Reverse Phase Cation Exchange Chromatography in Citrate Media" for submission to Radiochimica Acta (2022) (under internal review).

J. G. Mwakisege, G. Schweitzer and S. Mirzadeh, "Synthesis and Stability of Actinium-225 Endohedral Fullerenes, $^{225}Ac@C_{60}$", ACS Omega 5(42):27016-27025, October 2020, DOI:10.1021/acsomega.0c01659.

S. Mirzadeh, "Innovation, Impact and Strategic Importance of Alpha Emitting Radionuclides", Journal of Medical Imaging and Radiation Sciences, **50**, S6-S10 (2019).

L. Królicki, F. Bruchertseifer, J. Kunikowska, H. Koziara, B. Królicki, M. Jakuciński, D. Pawlak, C. Apostolidis, S. Mirzadeh, R. Rola, A. Merlo, A. Morgenstern, "Safety and efficacy of targeted alpha therapy with 213Bi-DOTA-substance P in recurrent glioblastoma", European Journal of Nuclear Medicine and Molecular Imaging, 46(3):614-622 (2019).

Kathleen Broderick, Rita Lusk, James Hinderer, Justin Griswold[1], Rose Boll, Marc Garland, Lawrence Heilbronn, and Saed Mirzadeh, "Reactor Production of Promethium-147", Applied Radiation and Isotopes, **144**, 54-63 (2018)

M. Toro González, D. M. Clifford, R. Copping, S. Mirzadeh, J. V. Rojas, "Synthesis and Characterization of Intrinsically Radiolabeled Lanthanide Phosphate Nanoparticles Toward Biomedical and Environmental Applications", J. Nanoparticle Research, **20 (**238), article id. 238, 15 pp (2018).

M. Toro González, R. Copping, S. Mirzadeh, J. V. Rojas, "Multifunctional $GdVO_4$: Eu Core-Shell Nanoparticles containing ^{225}Ac for Targeted Alpha Therapy and Molecular Imaging. J. Materials Chemistry B, 6, 7985- 7997 (2018)

Jonathan M. Fitzsimmons, Bryna Torre, Bryan James Foley, Roy Copping, David E. Hill, Saed Mirzadeh, Cathy S. Cutler, Leonard Mausner, and Dmitri Medvedev, "Evaluation of SynPhase Lanterns for capturing Ac-225 from bulk thorium", Journal of Radioanalytical and Nuclear Chemistry, 318 (1), 477-483 (2018).

L. Krolicki, F. Bruchertseifer, J. Kunikowska, H. Koziara, B. Królicki, M. Jakuciński, D. Pawlak, C. Apostolidis, S. Mirzadeh, R. Rola, A. Merlo, A. Morgenstern, Prolonged survival in secondary glioblastoma following local injection of targeted alpha therapy with ^{213}Bi-substance P analogue, European Journal of Nuclear Medicine and Molecular Imaging, **45**(9), 1636-1636 (2018)

Justin R. Griswold, Cara U. Jost, Daniel W. Stracener, Stephanie H. Bruffey, David Denton, Marc Garland, Lawrence Heilbronn, and Saed Mirzadeh, "Production of ^{229}Th for Medical Applications: Excitation Functions of Low-Energy Protons on ^{232}Th Targets", Physical Review C **98**, 044607 (2018).

AdvanCell
Ex. 1002 - Page 96

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Publications in referred journals

Michael E. Autenrieth, Christof Seidl, Frank Bruchertseifer, Thomas Horn, Florian Kurtz, Benedikt Feuerecker, Calogero D'Alessandria, Christian Pfob, Christos Apostolidis, Jürgen E. Gschwend, Markus Schwaiger, Klemens Scheidhauer, Saed Mirzadeh and Alfred Morgenstern, "Treatment of carcinoma *in situ* of the urinary bladder with an alpha-emitter immunoconjugate targeting the epidermal growth factor receptor: A pilot study", European Journal of Nuclear Medicine and Molecular Imaging, **45**(8):1364-1371 (2018)

Li, M., Zhang, X.; Quinn, T. P., Lee, D., Liu, D., Kunkel, F.; Zimmerman, B. E., McAlister, D., Olewein, K., Menda, Y., Mirzadeh, S., Copping, R., Johnson, F. L., Schultz, M. K., Automated cassette-based production of high specific activity [203/212Pb]peptide-based theragnostic radiopharmaceuticals for image-guided radionuclide therapy for cancer. Applied Radiation and Isotopes, **127**, 52-60 (2017).

Radchenko, V., Mastren, T., Meyer, C. A. L., Ivanov, A. S., Bryantsev, V. S., Copping, R., Denton, D., Engle, J. W., Griswold, J. R., Murphy, K., Wilson, J. J., Owens, A.; Wyant, L.; Birnbaum, E. R.; Fitzsimmons, J.; Medvedev, D.; Cutler, C. S.; Mausner, L. F., Nortier, M. F., John, K. D., Mirzadeh, S., Fassbender, M. E., Radiometric evaluation of diglycolamide resins for the chromatographic separation of actinium from fission product lanthanides. Talanta, **175**, 318-324 (2017)

Jelenska, J., Davern, S., Standaert, R., Mirzadeh, S., Greenberg, J-T., "Flagellin peptide flg22 gains access to long-distance trafficking in Arabidopsis via its receptor, FLS2" Journal of Experimental Botany, Vol. **68**, 1769 (2017).

J. R. Griswold, D. G. Medvedev, J. W. Engle, R. Copping, J. M. Fitzsimmons, V. Radchenko, J. C. Cooley, M. E. Fassbender, D. L. Denton, K. E. Murphy, A. C. Owens, E. R. Birnbaum, K. D. John, F. M. Nortier, D. W. Stracener, L. H. Heilbronn, L. F. Mausner, S. Mirzadeh, "Large Scale Accelerator Production of ^{225}Ac: Effective Cross Sections for 78-192 MeV Protons Incident on ^{232}Th Targets", Applied Radiation and Isotopes, **118**, 366-374 2016.

Susan Hogle, Rose Ann Boll, Karen Murphy, David Denton, Allison Owens, Tamara J. Haverlock, Marc Garland, and Saed Mirzadeh, "Reactor Production of Thorium-229", Applied Radiation and Isotopes, **114**, 19-27, 2016.

Sandra M. Davern, Timothy E. McKnight, Robert F. Standaert, Jennifer L. Morrell-Falvey, Elena D. Shpak, Udaya C. Kalluri, Joanna Jelenska, Jean T. Greenberg and Saed Mirzadeh, "Carbon Nanofiber Arrays: A Novel Tool for Microdelivery of Biomolecules to Plants", PLoS ONE, DOI:10.1371/journal.pone.0153621, pp1-26, April 27, 2016.

Justin Jeet, Christian Schneider, Scott T. Sullivan, Wade G. Rellergert, Saed Mirzadeh, A. Cassanho, H. P. Jenssen, Eugene V. Tkalya, and Eric R. Hudson, "Results of a direct search using synchrotron radiation for the low-energy ^{229}Th nuclear isomeric transition", Phys. Rev. Lett, **114**, 253001(1-6) (2015).

Jessika V. Rojas, Jonathan Woodward, Nan Chen, Adam J. Rondinone, Carlos H. Castano, and Saed Mirzadeh, (2015) "Synthesis and characterization of lanthanum phosphate nanoparticles as carriers for ^{223}Ra and ^{225}Ra for targeted alpha therapy", J. Nucl. Med. Biology, **42,** 614-620 (2015).

AdvanCell
Ex. 1002 - Page 97

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Publications in referred journals

Mark F. McLaughlin, David Robertson, Paul H. Pevsner, Jonathan S. Wall, Saed Mirzadeh, and Stephen J. Kennel, "LnPO4 nanoparticles doped with Ac-225 and sequestered daughters for targeted alpha therapy", Cancer Biotherapy and Radiopharmaceuticals. **29**(1), 34-41, (2014).

Mark F. McLaughlin, Jonathan Woodward, Rose A. Boll, Adam J. Rondinone, Saed Mirzadeh, and J. David Robertson, "Gold-Coated Lanthanide Phosphate Nanoparticles for an ^{225}Ac in vivo Alpha Generator", Radiochimica Acta, **101**, 595-600, (2013).

Delmau L. L., Moine J.M., Mirzadeh S., and Moyer B. A. (2013) "First Experimentally Determined Thermodynamic Values of Francium: Hydration Energy, Energy of Partitioning, and Thermodynamic Radius", J. Physical Chemistry B; **117**(31), 9258-9261.

McLaughlin M. F., Woodward J., Boll R.A., Wall J. S., Rondinone A. J., Kennel S. J., Mirzadeh S., and Robertson J.D., "Gold Coated Lanthanide Phosphate Nanoparticles for Targeted Alpha Generator Radiotherapy" PLOS One, 8/1, e54531 (2013).

Woodward J., Kennel S.J., Stuckey A., Osborne D., Wall J., Rondinone A., Standaert R.F., and Mirzadeh S., 2011,"LaPO4 Nanoparticles Doped with Actinium-225 that Partially Sequester Daughter Radionuclides", Bioconjugate Chemistry, **22**, 766-776 (2011).

Kennel, S. J., Woodward, J. D., Rondinone, A. J., Wall, J., Huang, Y, Mirzadeh, S., "The Fate of MAb targeted Cd^{125m}Te/ZnS nanoparticles *in vivo*", J. Nucl. Med. Biology, **35***, Issue 4*, *May 2008*, *Pages 501-514*

Diener, M. D., Alford, J. M., Kennel, S. J., Mirzadeh, S., "^{212}Pb@C_{60} and its Water-Soluble Derivatives: Synthesis, Stability and Suitability for Radioimmunotherapy", J. Am. Chem. Soc., **129**, 5131 (2007).

Diener, M. D., Alford, J. M., Williamson, K. A., Mirzadeh, S. "^{177}Lu @C_{60} and its Water-Soluble Derivatives: Production, Purification and Potential for Radioimmunotherapy", Chem. Phys. Lett (2007). (submitted).

Woodward, J. D., Kennel, S. J., Mirzadeh, S., Dai, S., Wall, J., Richey T., Avenell, J., Rondinone, A. J., "In vivo SPECT/CT imaging and biodistribution using radioactive Cd125mTe/ZnS nanoparticle", Nanotechnology **18**, 175103 - 175108 (2007).

Kennel, S., Lankford, T., Garland, M, Sundberg, J., P., Mirzadeh, S., "Biodistribution of ^{225}Ra citrate in mice: retention of daughter radioisotopes in bone", Nuclear Medicine and Biology, **32**, 859-867 (2005).

Boll, R. A., Malkemus, D., and Mirzadeh, S. "Production of Actinium-225 for Alpha Particle Mediated Radioimmunotherapy". *Applied Radiation and Isotopes*, **62**, pp 667-679 (2005).

Haverlock, T. J., Mirzadeh, S., and Moyer, B. A., "Selectivity of Calix [4] arene-bis(benzocrown-6) in the Complexation and Transport of Francium Ions", *Journal of American Chemical Society*, **125**, 1126-1127 (2003).

Garland, M. A., Mirzadeh, S., Alexander, C. W., Hirtz, G. J., Hobbs, R. W., and Knapp, F. F. Jr., "Flux Characterization of a Peripheral Target Position in the High Flux Isotope Reactor", *Applied Radiation and Isotopes,* **59**, 63-72 (2003).

AdvanCell
Ex. 1002 - Page 98

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Publications in referred journals

Mirzadeh, S., Lambrecht, F. Y., Lambrecht, R. M., "Decay of Tungsten-189", *Applied Radiation and Isotopes B Richard Lambrecht Memorial Issue*, **56**, 637-640 (2002).

Kennel, S. J., Mirzadeh, S., Eckelman, W. C., Waldmann, T. A., Garmastani, K., Yordanov, A. T., Stabin, M., and Brechbiel, M. W., "Vascular Targeted Radioimmunotherapy with the □-emitter ^{211}At", *Radiation Research*, **157**, 633-641 (2002).

Kennel, S. J., Brechbiel, M. W., Milenic, D. E., Schlom, J., and Mirzadeh, S. "Actinium-225 Conjugates of Mab CC49 and Humanized DCH2CC49: Therapy of LS174T Tumors in Nude Mice", *Cancer Biotherapy and Radiopharmaceuticals*, **17**, 219-231 (2002).

Kennel, S. J., Lankford, T. K., Davern, S., Foote, L., Taniguchi, K., Ohizumi, I., Tsutsumi, Y., Nakagawa, S., Mayumi, T., and Mirzadeh, S., ATherapy of Rat Tracheal Carcinoma IC-12 in SCID Mice: Vascular Targeting with Bi-213-MAb TES-23", European Journal of Cancer, 38, 1278-1287 (2002).

Milenic, D. E., Roselli, M., Mirzadeh, S., Pippin, G. C., Gansow, O. A., Cocher, D., Brechbiel, M. W., and Schlom, J. 'In Vivo Evaluation of Bismuth-Labeled Monoclonal Antibody Comparing DTPA-Derived Bifunctional Chelates", *Cancer Biotherapy and Radiopharmaceuticals*, **16**, 133-146 (2001).

Mirzadeh, S., Du, M., Beets, A., Knapp, F. F. Jr., "Thermo-separation of Neutron Irradiated Tungsten from Re and Os", *Industrial and Engineering Chemistry Research*, **39**, 3169-3172 (2000).

Kennel, S. J., Chappell, L. L., Dadachova, K., Brechbiel, M. W., Lankford, T. K., Davis, I. A., Stabin, M., and Mirzadeh, S., "Evaluation of ^{225}Ac for Vascular Targeted Radioimmunotherapy of Lung Tumors", *Cancer Biotherapy and Radiopharmaceuticals*, **15**, 235-244 (2000).

Kennel, S. J., Mirzadeh, S., Hurst, G. B., Foote, L. J., Lankford, T. K., Glowienka, K. A., Chappell, L. L., Kelso, J. R., Davern, S. M., Safavy, A., Brechbiel, M. W., "Labeling and Distribution of Linear Peptides Identified Using in-vivo Phage Display Selection for Tumors", *Journal of Nuclear Medicine and Biology*, **27**, 815-825 (2000).

Cagle, D. W., Kennel, S. J., Mirzadeh, S., Alford, M. J., Wilson L. J., "*In vivo* Studies of Fullerene-based Materials Using Endohedral Metallofullerene Radiotracer" *Proceedings of National Academy of Sciences*, **96**, 5182-5187 (1999).

Wilson, L. J., Cagle, D. W., Thrash, T. P., Kennel, S. J., Mirzadeh, S., Alford, M. J., Ehrhardt, G. J, "Metallofullerene Drug Design", *Coordination Chemistry Reviews*, **190**, 199 (1999)

Thrash, T. P., Cagle D. W., Alford, J. M., Wright, K., Ehrhardt, G. J., Mirzadeh, S., Wilson L. J., "Toward Fullerene-Based Radiopharmaceuticals: High Yield Neutron Activation of Endohedral ^{165}Ho Metallofullerenes", *Chemical Physics Letter*, 12673 (1999).

Kennel, S. J., Lankford, P. K., Foote. L. J., Davis, I. A., Boll, R. A., and Mirzadeh, S., "Combination Vascular Targeted and Tumor Targeted Radioimmunotherapy", *Cancer Biotherapy and Radiopharmaceuticals*, **14**, 371-379 (1999).

AdvanCell
Ex. 1002 - Page 99

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Publications in referred journals

Deal, K. A., Davis, I. A., Mirzadeh, S., Kennel, S. J., Brechbiel, M. W. "Improved *In Vivo* Stability of Actinium-225 Complexes", Journal *of Medicinal Chemistry*, **42**, 2988-2992 (1999).

Davis, I. A., Glowienka, K. A., Boll, R. A., Deal, R. A., Brechbiel, M. W., Stabin, M, Bochsler, P. N., Mirzadeh, S., Kennel, S. J., "Comparison of Actinium-225 Chelates: Tissue Distribution and Radiotoxicity", Journal *of Nuclear Medicine and Biology*, **26**, 581-589 (1999).

Kennel, S. J., Boll, R., Stabin, M., Schuller, H. M. and Mirzadeh, S., "Radioimmunotherapy of Micrometastases in Lung with Vascular Targeted ^{213}Bi", *British Journal of Cancer* **80**, 175-184 (1999).

Kennel, S. J., Stabin, M., Foote. L. J., Lankford, P. K., Terzaghi-Howe, M., Patterson, H., Barkenbus, J, Popp, D. M. and Mirzadeh, S., "Toxicity and Microdosimetry for ^{213}Bi Bound to Membranes of Monolayer and Spheroid Cultures of Tumor Cells", *Radiation Research*, **151**, 244-256 (1999).

Kennel, S. J., Stabin, M., Yoriyaz, H., Brechbiel, M., and Mirzadeh, S., "Treatment of Lung Tumor Colonies with ^{90}Y Targeted to Blood Vessel - Comparison with the α-particle Emitter ^{213}Bi", *Journal of Nuclear Medicine and Biology*, **26**, 149-157 (1999).

Roselli, M., D. E. Milenic, S. Mirzadeh, M. Brechbiel, C. G. Pippin, O. A. Gansow, D. Colcher, and J. Schlom. "Biodistribution Studies of Indium-111 and Yttrium-Labeled MAB B72.3 using DTPA-derived Bifunctional Chelates ", *Journal of International Society of Tumor Targeting*. **1**, 20-40 (1999).

Roselli, M., D. E. Milenic, M. Brechbiel, S. Mirzadeh, C. G. Pippin, O. A. Gansow, D. Colcher, and J. Schlom, "In Vivo Comparison of CHX-DTPA Ligand Isomers in Athymic Mice Bearing Carcinoma Xenografts", Cancer Biotherapy and Radiopharmaceuticals 14(3):209-20, 1999.

McMurry, T. J., Pippin, G. C., Wu, C., Kim, D. A., Brechbiel, M. W., Mirzadeh, S., and Gansow, O. A., "Physical Parameters and Biological Stability of Yttrium (III) Diethylenetriaminepentaacetic Acid Derivative Conjugates" *Journal of Medicinal Chemistry,* **41**, 3546-3549 (1998).

Kennel, S. J. and Mirzadeh, S., "Vascular Targeting for Radioimmunotherapy with ^{213}Bi -- an Alpha Particle Emitter", *Journal of Nuclear Medicine and Biology*, **25**, 241-246 (1998).

Wang, S. J., Lin, W. Y., Chen, M. N., Hsieh, B. T., Mirzadeh, S., Knapp, F. F. , Jr., "Rhenium-188 Microspheres: A new Radiation Synovectomy Agent", *Nuclear Medicine Communications*, **19**, 427-433 (1998).

Wang, S. J., Lin, W. Y., Chen, M. N., Hsieh, B. T., Mirzadeh, S., Knapp, F. F., Jr., "Intratumoral Injection of Rhenium-188 Microspheres into an Animal Model of Hepatoma", *Journal of Nuclear Medicine*, **39**, 1752-1757 (1998).

Boll, R. A., Mirzadeh, S. and Kennel, S. J. (1997), "Optimization of Radiolabeling of Immunoproteins with ^{213}Bi", Radiochimica Acta **79**, 145-149.

Mirzadeh, S. and Walsh, P., "Numerical Evaluation of the Production of Radionuclides in a Nuclear Reactor -- Part I", Applied *Radiation and Isotopes*, **49**, 379-382 (1997).

AdvanCell
Ex. 1002 - Page 100

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Publications in referred journals

Mirzadeh, S. and Walsh, P., "Numerical Evaluation of the Production of Radionuclides in a Nuclear Reactor -- Part II", Applied *Radiation and Isotopes*, **49**, 383-395 (1997).

Mirzadeh, S., Knapp, F. F., Jr. and Lambrecht, R. M., "Burn-up cross-section of W-188", *Radiochimica Acta, 77*, 99-102 (1997).

Dadachova, E. and Mirzadeh, S., "The Role of Tin in Direct Labeling of Proteins with Rhenium-188", *J. Nuclear Medicine and Biology, **6**,* 605-608 (1997).

Mirzadeh, S., C. W. Alexander and F. F. Knapp, Jr., "Evaluation of Neutron Inelastic Scattering, [n,n'], for Production of High Spin ^{117m}Sn, ^{119m}Sn and ^{195m}Pt Isotopes", *Applied Radiation and Isotopes*, **48**, 441-446 (1997).

Dadachova, E., Mirzadeh, S., Smith, S. V., Knapp, F. F. Jr. and Hetherington, E. L. "Radiolabeling Antibodies with Holmium-166", *Applied Radiation and Isotopes* **48**, 477-481 (1997).

Dadachova, E., Mirzadeh, S. and Lambrecht, R. M., "Tungstate-Ion-Alumina Interaction in a ^{188}W/^{188}Re Biomedical Generator", *Journal of Physical Chemistry* **99**, 10976-10981 (1995).

Smith, S. V., Di Bartolo, N, Mirzadeh, S., Lambrecht, R. M. and Knapp, F. F. Jr., "[^{166}Dy] Dysprosium/[^{166}Ho] Holmium *In Vivo* Generator", Applied *Radiation and Isotopes* **46**, 759-764 (1995).

Dadachova, E., Mirzadeh, S., Lambrecht, R. M., Hetherington, E. and Knapp, F. F., "Separation of Carrier-free ^{166}Ho from Dy_2O_3 Targets by Partition Chromatography and Electrophoresis", *Journal of Radioanalytical and Nuclear Chemistry - Letters*, **199**, 115 (1995).

Dadachova, E., Mirzadeh, S., Lambrecht, R. M., Hetherington, E. and Knapp, F. F., "Separation of Carrier-free Holmium-166 from Neutron-irradiated Dysprosium Targets", *Journal of Analytical Chemistry*, **66**, 4272-4277 (1994).

Knapp, F. F., Jr., Callahan, A. P., Beets, A. L., Mirzadeh, S., and Hsieh. B.-T. "Processing of Reactor-Produced Tungsten-188 for Fabrication of Clinical Scale Alumina-Based Tungsten-188/Rhenium-188 Generators" Applied *Radiation and Isotopes*, **45**, 1123-1128 (1994).

Kamioki, H., Mirzadeh, S., Lambrecht, R. M., Knapp, F. F. and Dadachova, E., "^{188}W6^{188}Re Generator for Biomedical Applications", *Radiochimica Acta*, 65, 39-46 (1994).

Junghans, R. P., Dobbs, D., Raubitschek, A. A., Brechbiel, M. W., Mirzadeh, S., Gansow, O. A. and Waldmann, T. A., "Pharmacokinetics and Bioactivity of DOTA-Bismuth Conjugated Anti-Tac Antibody for Alpha Emitter Therapy", *Cancer Research*, **53**, 5683-9 (1993).

Mirzadeh, S., K. Kumar and O. A. Gansow, "The Chemical Fate of ^{212}Bi-DOTA Formed by ß-Decay of ^{212}Pb(DOTA)$^{2-}$ Complex", *Radiochimica Acta*, **60**,1-10 (1993).

AdvanCell
Ex. 1002 - Page 101

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Publications in referred journals

Lisic, E. C., S. Mirzadeh, F. F. Knapp, Jr., "Synthesis of Carrier-free Rhenium-188(V)DMSA Using Triphenyl Phosphine as a Facile Reducing Agent", *Journal of Labeled Compounds and Radiopharmaceuticals* **XXXIII**, 65-76 (1993).

Mirzadeh, S. and F. F. Knapp, Jr., "Spontaneous Electrochemical Separation of Carrier-free ^{64}Cu and ^{67}Cu from Zn Targets", *Radiochimica Acta*, **57**, 193-199 (1992).

Mausner, L. F., S. Mirzadeh, and S. C. Srivastava "Improved Specific Activity of ^{117m}Sn with the Szilard-Chalmers Process", Applied *Radiation and Isotopes* **43**, 1117-1122 (1992).

Mirzadeh, S., D. E. Rice and F. F. Knapp, Jr., "Carrier-free ^{194}Ir from an ^{194}Os/^{194}Ir Generator - A New Candidate for Radioimmunotherapy", *Applied Radiation and Isotopes* **43**, 689-692(1992).

Roselli, M., J. Schlom, O. A. Gansow, M. Brechbiel, S. Mirzadeh, C. G. Pippin, D. E. Milenic and D. Colcher. "Comparative Biodistribution Studies of DTPA-derivative Bifunctional Chelates for Radiometal Labeled Monoclonal Antibodies", *Nuclear Medicine and Biology* **18**, 389-394 (1991).

Brechbiel, M, S. Mirzadeh, O. A. Gansow, "Backbone-substituted DTPA-Ligands for Radioimmunotherapy with Yttrium-90", *Bioconjugate Chemistry* **2,** 187-189 (1991).

Coursey B. M., J. M. Calhoun, J. Cessna, D. D. Hoppe, A. P. Callahan, S. Mirzadeh, and F. F. Knapp, Jr., "Assay of the Eluent from the Alumina-Based Tungsten-188/Rhenium-188 Generator", *Journal of Radiochemistry and Radioisotopes* **1**, No. 4, 38-49 (1990).

Mirzadeh, S., M. W. Brechbiel, and O. A. Gansow, "Radiometal Labeling of Immunoproteins: Covalent Linkage of 2-(4-isothiocyanatobenzyl)-DTPA to Immunoglobulin", *Bioconjugate Chemistry* **1**, 59-65 (1990).

Cooper, M. M., R. C. Roberts, C. K. Goldman, S. Mirzadeh, C. Stone, O. A. Gansow, R. E. Clark and T. A. Waldmann, "Use of Yttrium-90-labeled Anti-Tac Antibody in Primate Xenograft Transplantation", *Journal of Transplantation* **50,** 760-765 (1990).

Ruegg, C. L., W. T. Anderson-Berg, M. W. Brechbiel, S. Mirzadeh, O. A. Gansow and M. Strand, "Improved *in vivo* Stability and Tumor Targeting of Bismuth-Labeled Antibody", *Cancer Research* **50**, 4221-4226 (1990).

Mausner, L. F., S. Mirzadeh, H. Schnakenberg and S. C. Srivastava, "The Design and Operation of the Upgraded BLIP Facility for Radionuclide Research and Production", *Applied Radiation and Isotopes* **41**, 367-374 (1990).

Kozak, R. W., A. Raubitschek, S. Mirzadeh, M. W. Brechbiel, R. Junghans, O. A. Gansow, and T. A. Waldmann, "The Nature of the Bifunctional Chelating Agent Used for Radioimmunotherapy with Yttrium-90 Monoclonal Antibodies as a Critical Factor in Determining *In Vivo* Survival and Organ Toxicity", *Cancer Research*, **49**, 2639-2644 (1989).

AdvanCell
Ex. 1002 - Page 102

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Publications in referred journals

Roselli, M., J. Schlom, O. A. Gansow, A. Raubitschek, S. Mirzadeh, M. Brechbiel and D. Colcher. "Comparative Biodistribution of Yttrium and Indium Labeled Monoclonal Antibody B72.3 in Athymic Mice Bearing Human Colon Carcinoma Xenografts", *Journal of Nuclear Medicine*, **30**, 672-682 (1989).

Mirzadeh, S. and M. Kahn, "Studies of the Chemical Behavior of Carrier-free Ge-68: III. Adsorptive Properties", *Radiochimica Acta*, **39**, 189 (1986).

Mirzadeh, S., Y. Y. Chu, S. Katcoff, and L. K. Peker, "Decay of 7.1-min Th-235", *Journal of Physical Review C*, **33**, 2159 (1986).

Mirzadeh, S. and M. Kahn, "Studies of the Chemical Behavior of Carrier-free Ge-68: II. A Determination of the Distribution Constant from the Distillation of the Azeotropic HCl", *Radiochimica Acta*, **39**, 73 (1986).

Mausner, L. F., S. C. Srivastava, S. Mirzadeh, G. E. Meinken, and T. Prach, "I-123 Research and Production at Brookhaven", *International Journal of Applied Radiation and Isotopes*, **37**, 843 (1986).

Mausner, L. F., S. Mirzadeh, and T. E. Ward, "Nuclear Data for Production of Sn-117m for Biomedical Applications", *Journal of Radiation Effects*, **94**, 59 (1986).

Mirzadeh, S., L. F. Mausner, and S. C. Srivastava, "Production of No-carrier-added Cu-67", *International Journal of Applied Radiation and Isotopes*, **37**, 29, (1986).

Lambrecht, R. M. and S. Mirzadeh, "Cyclotron Isotopes and Radiopharmaceuticals, XXXV. Astatine-211", *International Journal of Applied Radiation and Isotopes*, **36**, 443 (1985).

Lambrecht, R. M. and S. Mirzadeh, "Astatine-211: Production, Radiochemistry and Nuclear Data", *Journal of Labeled Compounds and Radiopharmaceuticals*, **11**, 1288-1289 (1984).

Bloomer, W. D., W. H. McLaughlin, R. M. Lambrecht, R. W. Atcher, S. Mirzadeh, J. L. Madara, R. A. Milius, M. R. Zalutsky, S. J. Adelstein, and A. P. Wolf, "At-211 Radiocolloid Therapy: Further Observations and Comparisons with Radiocolloids of P-32, Dy-165, and Y-90", *International Journal of Radiation Oncology and Biological Physics*, **10**, 341 (1984).

Mirzadeh, S., Y. Y. Chu, S. Katcoff, and L. K. Peker, "Decay of 37.5-min Th-236 and 9.l-min Pa-236", *Journal of Physical Review C*, **29**, 985 (1984).

Mirzadeh, S., P. P. Parekh, S. Katcoff, and Y. Y. Chu, "Cross-section Systematics for Nuclide Production at a Medium Energy Spallation Neutron Facility", *Journal of Nuclear Instruments and Methods*, **216**, 149 (1983).

Bloomer, W. D., W. H. McLaughlin, R. Milius, M. R. Zalutsky, S. J. Adelstein, S. Mirzadeh, R. M. Lambrecht, and A. P. Wolf, "Astatine-211: Optimization for Production of Inorganic Radiopharmaceuticals", *Journal of Nuclear Medicine*, **24**, P122 (1983).

Mirzadeh, S. and Y. Y. Chu, "A Rapid Radiochemical Separation Procedure for Mercury from Lead and Bismuth Targets", *Radiochemical and Radioanalytical Letters*, **51**, 279 (1982).

AdvanCell
Ex. 1002 - Page 103

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Publications in referred journals

Mirzadeh, S., M. Kahn, P. Grant, and H. A. O'Brien, Jr., "Studies of the Chemical Behavior of Carrier-free Ge-68: I. Purification by Distillation from Acidic Chloride Solutions", *Radiochimica Acta*, **28**, 47 (1981).

Mirzadeh, S., M. Kahn, P. Grant, and H. A. O'Brien, Jr., "A Procedure for the Preparation of Chloride-free Solution of Carrier-free Ge-68", *Radiochemical Radioanalytical Letters*, **42**, 361 (1980).

Grant, P. M., H. A. O'Brien, Jr., and S. Mirzadeh, "Premature Evaluation of a Ge(68)-Ga(68) Distillation Generator", *Journal of Nuclear Medicine*, **21**, 702 (1980).

AdvanCell
Ex. 1002 - Page 104

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Awarded Patents

DePaoli D. W., Hu, M. Z., Mirzadeh, S. and Clavier, J. W, "Inorganic Resin For Clinical Use of Bismuth-213 Generators", U. S. Patent7,914,766 B1, March, 29, 2011.

Mirzadeh, S. and Garland, M., "Production of Thorium-229 Using Helium Nuclei" U. S. Patent 7,852,975 B2, December 14, 2010.

Knapp, F. F., Boll, R.A., Mirzadeh, S., "Chromatographic Extraction with Di(2-EthyHexyl)-orthophosphoric Acid for Production and Purification of Promethium-147", U.S. Patent 7,435,399 B2, October 14, 2008.

Mirzadeh, S., Du, M., Beets, A. L. and Knapp, F. F., "Method for Preparation of High Specific Activity Platinum-195m for Medical Therapy", U. S. Patent 6,751,280, June 15, 2004.

Mirzadeh, S., Du, M., Beets, A. L, and Knapp, F. F., "Method for Preparing High Specific Activity Lutetium-177 ", U. S. Patent 6.716,353 B1, April 6, 2004.

Mirzadeh, S., Knapp, F. F. Jr., and Collins, E. D. "*A tandem generator for preparation of highly concentrated ^{99}Tc from low specific activity of ^{99}Mo*" U. S. Patent No., 5,729,821, March 1998.

Beets, A. L., Mirzadeh, S., Knapp, F. F. and Guhlke, S., "Concentration of Perrhenate and Pertechnetate Solutions", U.S. Patent No. 5,774,782, June 1998.

Knapp, F. F., E. C. Lisic, S. Mirzadeh, and A. P. Callahan, "*Tungsten-188/Carrier-free Re-188 Perrhenic Acid Generator System*", U.S. Patent No. 5,186,913, April 26, 1991.

Mirzadeh, S. and R. M. Lambrecht, "*Methods for the Simultaneous Preparation of Radon-211 and Xe-125, Astatine-211, Iodine-125 and Iodine-123*", U.S. Patent No. 4,644,869, May 12, 1987.

Mirzadeh, S. and R. M. Lambrecht, "*Process for Producing Astatine-211 for Radiopharmaceutical Use*", U.S. Patent No. 4,681,727, July 21, 1987.

Mirzadeh, S., R. E. Whipple, P. M. Grant, H. A. O'Brien, Jr., "*Evaporation-Based Ge/Ga(68) Separation*", U.S. Patent No. 4,268,730, February 3, 1981.

Patent Applications

Mirzadeh, S. and Garland, M., "Production of Thorium-229 from Radium-228", U.S. Patent Application Serial No. 11/507,168, Filing date: August 21, 2006 (UTB #1273.2). Not granted

Mirzadeh, S. and Garland, M., "Production of Thorium-229 from Thorium-230", U.S. Patent Application Serial No. 11/507,152, Filing date: August 21, 2006 (UTB# 1273.3.). Not granted

Mirzadeh, S. and Garland, M., "Production of Thorium-229 from Radium-226 Using Epithermal and Higher Energy Neutron Irradiation". Filing date, July, 2007 (UTB# 1273.5). Not granted

Docusign Envelope ID: 2EC499A6-CDCE-4599-AD9E-B0F25C9CA642

Mirzadeh, S., Aaron, S., and Zevenbergen, L. "A New Indium-114m Brachytherapy Source", U. S. Patent Application (1999). Not granted

Mirzadeh, S. and Kennel, S. J., "Vascular Targeting of Alpha Particle Emitting Radioisotopes for Radiotherapy", U.S. Patent Application (1998). Not granted