Use of 55 PET radiotracers under approval of a Radioactive Drug Research Committee (RDRC)

Isaac M. Jackson1,2, So Jeong Lee1,3, Alexandra R. Sowa1, Melissa E. Rodnick1, Laura Bruton1, Mara Clark1, Sean Preshlock1, Jill Rothley1, Virginia E. Rogers1, Leslie E. Botti1, Bradford D. Henderson1, Brian G. Hockley1, Jovany Torres1, David M. Raffel1, Allen F. Brooks1, Kirk A. Frey1, Michael R. Kilbourn1, Robert A. Koeppe1, Xia Shao1 and Peter J. H. Scott1*

* Correspondence: pjhscott@med.umich.edu
This article is dedicated to Capt. Richard Fejka, MS, RPh, BCNP, USPHS (Ret.) on the occasion of his retirement after 39 years of government service and 17 years overseeing the RDRC Program at the U.S. Food and Drug Administration.

1Department of Radiology, University of Michigan, 2276 Medical Science Bldg I, SPC 5610, Ann Arbor, MI 48109, USA
Full list of author information is available at the end of the article

Abstract

Background: In the US, EU and elsewhere, basic clinical research studies with positron emission tomography (PET) radiotracers that are generally recognized as safe and effective (GRASE) can often be conducted under institutional approval. For example, in the United States, such research is conducted under the oversight of a Radioactive Drug Research Committee (RDRC) as long as certain requirements are met. Firstly, the research must be for basic science and cannot be intended for immediate therapeutic or diagnostic purposes, or to determine the safety and effectiveness of the PET radiotracer. Secondly, the PET radiotracer must be generally recognized as safe and effective. Specifically, the mass dose to be administered must not cause any clinically detectable pharmacological effect in humans, and the radiation dose to be administered must be the smallest dose practical to perform the study and not exceed regulatory dose limits within a 1-year period. In our experience, the main barrier to using a PET radiotracer under RDRC approval is accessing the required information about mass and radioactive dosing.

Results: The University of Michigan (UM) has a long history of using PET radiotracers in clinical research studies. Herein we provide dosing information for 55 radiotracers that will enable other PET Centers to use them under the approval of their own RDRC committees.

Conclusions: The data provided herein will streamline future RDRC approval, and facilitate further basic science investigation of 55 PET radiotracers that target functionally relevant biomarkers in high impact disease states.

Keywords: PET imaging, Regulatory oversight, Dosimetry, RDRC, IND, Radiopharmaceuticals, Quality assurance

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Background

Human use of positron emission tomography (PET) radiotracers in a given country (or member states in the case of the European Union) is required to be conducted under appropriate governmental oversight (Schwarz and Decristoforo 2019; Schwarz et al. 2019). In this paper, we focus upon clinical use of PET radiotracers in the United States, which is regulated by the Food and Drug Administration (FDA) (VanBrocklin 2008; Harapanhalli 2010; Schwarz et al. 2014). However, we expect the regulatory concepts described herein to also hold true in other locations, particularly in light of recent efforts to harmonize PET regulations around the world (Schwarz et al. 2019).

In the US, clinical use of PET radiotracers is conducted under the umbrella of an FDA-approved New Drug Application (NDA) or, in the case of generic PET radiotracers, an Abbreviated New Drug Application (ANDA). Human research is also conducted under governance of the FDA, via three major pathways: i) the Investigational New Drug application (IND), ii) an exploratory IND (eIND), or iii) under the oversight of a Radioactive Drug Research Committee (RDRC) (Suleiman et al. 2006; FDA Guidance for Industry and Researchers: The Radioactive Drug Research Committee: Human Research without an Investigational New Drug Application 2010; Carpenter Jr et al. 2009; Mosessian et al. 2014). The necessary path to approval is dictated by parameters outlined below, as well as the stated purpose of the research in question (Fig. 1).

While the IND and eIND represent the most common pathways to FDA approval for first-in-man studies, some of the requirements (e.g., costly toxicology in two species for an IND) represent significant hurdles to overcome in the application process. One notable solution, as described by Mosessian et al., is to divide labor and preparation for different components of the application between different cores and facilities at a given institution (Mosessian et al. 2014). In contrast, conducting human PET research under RDRC oversight represents a relatively efficient and cost effective path to FDA approval. The concept of the RDRC was introduced in 1975, and committees are charged by the FDA with the responsibility of overseeing PET research at the institutional level.

Fig. 1 Regulatory Oversight for PET Drugs in the United States
RDRC committees are comprised of at least 5 members and are required to include people with the following expertise:

- Physicians specializing in nuclear medicine;
- Nuclear pharmacists and/or radiochemists that are trained and qualified to formulate radioactive drugs;
- Persons having training in radiation safety and radiation dosimetry;
- Individuals specializing in disciplines pertinent to nuclear medicine (radiology, internal medicine, hematology, endocrinology, radiation therapy, clinical pharmacology, etc.).

In order for a given PET imaging study to be conducted under RDRC approval, the proposed research must meet the following criteria (as described comprehensively in 21 CFR 361.1):

- Stated purpose of the research must fall under the category of basic science, including but not limited to studies of: metabolism, kinetics, biodistribution, pathophysiology, biochemistry, transporter processes, and receptor binding/occupancy.
- The research cannot be intended for immediate therapeutic or diagnostic purposes, or to determine the safety and effectiveness of the PET radiotracer, but can have therapeutic/diagnostic implications. If at any point research initiated under RDRC approval shifts to directly address these subjects, IND approval must be obtained prior to further studies.
- The protocol must involve less than 30 patients, of age 18 or older (exceptions possible pending special approval), and women of child bearing potential must provide a written statement that they are not pregnant (without exception).
- The PET radiotracer is generally recognized as safe and effective (GRASE). Specifically:
  - The mass dose to be administered must not cause any clinically detectable pharmacological effect in humans. It is important to note that this generally precludes first-in-human testing of a PET radiotracer from being done under RDRC approval. Notably, RDRC approval can be used for study of radiolabeled endogenous molecules, as well as isotopic substitutions on clinically characterized compounds (i.e; substituting $^{18}\text{F}$ for $^{19}\text{F}$ on a small molecule ligand that has previously been approved and studied by the FDA, often via IND)
  - The radiation dose to be administered must be the smallest dose practical to perform a given study. Specifically, the radiation dose to an adult research subject from a single study, or cumulatively from a number of studies, conducted within 1 year may not exceed established regulatory dose limits:
    (a) Whole Body / Active Blood-Forming Organs / Lens of Eye / Gonads: Single Dose (Effective Dose) = 3 rem (0.03 Sv), Annual & Total Effective Dose Commitment = 5 rem (0.05 Sv);
    (b) Other Organs: Single Dose = 5 rem (0.05 Sv); Annual and Total Dose Commitment = 15 rem (0.15 Sv).

The radiation dose to a subject consists of the sum total of all sources of radiation associated with the research protocol, including the PET radiotracer(s),
associated x-ray procedures (including CT scans, PET transmission scans etc.) and any follow-up studies.

- For research subject under 18 years of age at his or her last birthday, the RDRC regulations require that the radiation limits do not exceed 10% of the radiation dose values given above.

- Other key criteria as described in 21 CFR 361.1 include providing evidence of:
  Qualified investigators, high quality of drug, research protocol, appropriate licensure to handle radioactive material, and review/approval for work with human subjects (via the Institutional Review Board (IRB)).

If all of these criteria are met, then the research can proceed following RDRC and IRB approval. Research conducted in RDRC studies is considered basic science. Specifically, basic science research is intended to advance scientific knowledge, but not to evaluate safety or efficacy of a PET radiotracer or to make clinical decisions. Failure to meet this, or any of the other RDRC criteria outlined above, necessitates that the research be conducted under an IND or eIND application that has been approved by the U.S. Food and Drug Administration (FDA), as outlined in 21 CFR 312 (Mosessian et al. 2014).

To ensure compliance with the pertinent regulations, FDA vests RDRC committees with oversight responsibility for basic science research conducted at the committee’s institution. The committee reviews and approves research protocols to ensure compliance with RDRC regulations, and submits annual reports to FDA that list committee members and summarize all studies conducted under the committee’s approval in the preceding year. The RDRC committee must also submit a special summary (Form FDA 2915) for any approved study involving > 30 research subjects (Suleiman et al. 2006).

Conducting human PET imaging under RDRC approval represents a straightforward and economical pathway to clinical use, particularly since there is no requirement for resource intensive pharmacology-toxicology studies. In our experience, the main barrier to using a PET radiotracer for basic science under RDRC approval is actually accessing the required information about pharmacological dose/mass and radioactive dose. For a given radiotracer this information can either come from the peer-reviewed scientific literature or other valid data, often in the form of a signed letter from an institution already working with the radiotracer in question. In an effort to remove barriers to those wishing to conduct clinical PET research under RDRC, herein we provide pharmacological dose and radioactive dosimetry details for 55 such PET radiotracers that will enable other PET Centers to use them under the approval of their own RDRC committees, eliminating the need to obtain a specific signed letter on a case-by-case basis. The article is made available Open Access in an attempt to further improve accessibility for our imaging colleagues, and we encourage other PET Centers with large clinical radiotracer portfolios to publish sister articles in the near future.

**Methods**

**Radiosyntheses**

PET radiotracers were commercially available, or synthesized according to the literature radiosyntheses referenced in Table 1 or novel radiosyntheses described in the Supporting Information. Production and quality control of all radiotracers was conducted
| Radiotracer Abbreviation | Application | Radiosynthesis | Dosimetry | Historical Imaging |
|------------------------|-------------|----------------|-----------|-------------------|
| $^{11}$C Acetate       | $^{[11C]}$ACE | Metabolism     | Runkle et al. 2011 | Seltzer et al. 2004 | Duvernoy et al. 2016 |
| $^{11}$C Aminocyclohexane carboxylic acid | $^{[11C]}$ACHC | Amino acid transport | Koeppe et al. 1990a | Washburn et al. 1982 | Koeppe et al. 1990a |
| $^{[11C]}$Methyl-4- piperidinyl n-butyrate | $^{[11C]}$BMP | Butyrylcholinesterase | Snyder et al. 2001 | Virta et al. 2008 | Kuhl et al. 2006 |
| $^{[11C]}$Butanol       | $^{[11C]}$BUT | Blood flow     | See Supporting Information | See Supporting Information | Quarles et al. 1993 |
| $^{[11C]}$Carfentanil  | $^{[11C]}$CFN | Mu opioid receptors | Blecha et al. 2017 | Newberg et al. 2009 | Zubiena et al. 2000 |
| $^{[11C]}$Choline       | $^{[11C]}$CHO | Choline biochemistry | Shao et al. 2014 | Tolvanen et al. 2010 | Piet et al. 2009 |
| $^{[11C]}$DASB          | $^{[11C]}$DASB | Serotonin transporter | Shao et al. 2014 | Lu et al. 2004 | Albin et al. 2008 |
| $^{[11C]}$Dihydrotetabenazine | $^{[11C]}$DTBZ | Vesicular monoamine transporter 2 (VMAT2) | Shao et al. 2014 | Murthy et al. 2008 | Koeppe et al. 1995 |
| $^{[11C]}$Epinephrine   | $^{[11C]}$EPI | Norepinephrine Transporter (NET) | Chakraborty et al. 1993 | Wrobel et al. 1997 | Münch et al. 2000 |
| $^{[11C]}$Flumazenil    | $^{[11C]}$FMZ | GABA<sub>A</sub> Receptors | Shao et al. 2011a | Laymon et al. 2012 | Koeppe et al. 1991 |
| $^{[11C]}$Meta-Hydroxyephedrine | $^{[11C]}$MHE | NET, Sympathetic nervous system | Shao et al. 2014 | Wrobel et al. 1997 and Supporting Information | Duvernoy et al. 2016 |
| $^{[11C]}$LY2795550     | $^{[11C]}$LY2795550 | Kappa opioid receptors | Yang et al. 2018 | See Supporting Information | Nagarawa et al. 2015 |
| $^{[11C]}$Methionine    | $^{[11C]}$MET | Amino acid | Shao et al. 2014 | Deloa et al. 1998 | Miller et al. 2019 |
| $^{[11C]}$Methoxytetrabenazine | $^{[11C]}$MTZB | VMAT2 | DaSilva et al. 1993a | Wrobel et al. 1997 | Vander Borght et al. 1995 |
| $^{[11C]}$Methylphenidate | $^{[11C]}$MPH | Dopamine transporter | Moran et al. 2010 | See Supporting Information | Albin et al. 2009 |
| $^{[11C]}$N-Methylpipеридинил benzilate | $^{[11C]}$NMBP | mACHR | Mulholland et al. 1995 | Mulholland et al. 1995 | Zubiena et al. 2001 |
| $^{[11C]}$OMAR/$^{[11C]}$JHU 755.28 | $^{[11C]}$OMAR | Cannabinoid 2 receptors | Shao et al. 2015 | Wong et al. 2010 | Wong et al. 2010 |
| $^{[11C]}$Palmitate     | $^{[11C]}$PALM | Fatty acid metabolism | Runkle et al. 2011 | Chistensen et al. 2017 | de Jong et al. 2009 |
| $^{[11C]}$PBR28         | $^{[11C]}$PBR28 | Translocator protein 18 kDa (TSPO) | Shao et al. 2014 | Brown et al. 2007 | Kreisl et al. 2016 |
| $^{[11C]}$Pittsburgh Compound B | $^{[11C]}$PBB | Amyloid plaques | Shao et al. 2014 | O’Keefe et al. 2009 | Burke et al. 2011 |
| $^{[11C]}$E-N-(3-iodoprop-2-eryl)-2β-(4′-tolyl) nortropane | $^{[11C]}$PET | Dopamine transporter | Doolé et al. 2000; Haildin et al. 2003 | Ribeiro et al. 2007 | Hallidin et al. 2003 |
| Radiotracer | Abbreviation | Application | Radiosynthesis | Dosimetry | Historical Imaging |
|------------|--------------|-------------|----------------|-----------|--------------------|
| [11C]Phenylephrine | [11C]PHEN | NET | Del Rosario et al. 1996 | Wrobel et al. 1997 | Raffel et al. 1996 |
| R(-)-[N-Methyl-11C]PK11195 | [11C]PK11195 | TSPO | Shao et al. 2014 | See Supporting Information | Junck et al. 1989 |
| [11C]PMP | [11C]PMP | Acetylcholinesterase | Shao et al. 2014 | Ribeiro et al. 2005 | Scott et al. 2006 |
| [11C]Raclopride | [11C]RAC | Dopamine D2 receptors | Shao et al. 2014 | see Supporting Information | Junck et al. 1989 |
| [11C]Ro-54,864 | [11C]Ro-54,864 | TSPO | Watkins et al. 1988 | Pient et al. 2017 | Pient et al. 2017 |
| [11C]Sarcosine | [11C]SARC | Sarcosine biochemistry | Piert et al. 2017 | Pient et al. 2017 | Pient et al. 2017 |
| [11C]Scopolamine | [11C]SCOP | mAChR | Mulholland et al. 1988 | Frey et al. 1992 | Frey et al. 1992 |
| [11C]Tetrahydrobenzine | [11C]THB | VMAT2 | DaSilva et al. 1993b | DaSilva et al. 1994 | Klibourn et al. 1993 |
| [11C]Tropanylbenzilate | [11C]TRB | mAChR | Mulholland et al. 1992 | Mulholland et al. 1992 | Koepp et al. 1994 |
| [11C]WAY-100635 | [11C]WAY | S-HT1a Receptor | Krasikova et al. 2009 | Parsley et al. 2005 | Micke et al. 2008 |

**[18F] Radiotracers**

| Radiotracer | Abbreviation | Application | Radiosynthesis | Dosimetry | Historical Imaging |
|-------------|--------------|-------------|----------------|-----------|--------------------|
| [18F]Flortaucipir | [18F]AV1451; [18F]TB07; Tauvid | Tau | Mills et al. 2017 | Choi et al. 2016 | Drake et al. 2019; Kramer et al. 2020 |
| 3-[1,4-Diazabicyclo[3.2.2]nonan-4-yl]-6-[18F]fluoro-dibenzo[b,d]thiophene 5,5-dioxide | [18F]FUJUB2132; [18F]FAEAM | α7 nicotinic acetylcholine receptor (nAChR) | Gao et al. 2013 and Supporting Information | Wong et al. 2014 and Supporting Information | b; Wong et al. 2014 |
| Fluciclovine (anti-1-Amino-3-[18F]-fluorocyclobutane-1-carboxylic acid) | [18F]FACBC; Auxumin | Amino acid transport | Törnsten et al. 2013 | Oye et al. 2007; McParland et al. 2010 | b; Songmen et al. 2019 |
| [18F]Fluoroamphetamine | [18F]FAA | Tumor hypoxia | Shao et al. 2011b | Savi et al. 2017 | Beck et al. 2007 |
| 2-[18F]Fluoro-2-deoxy-D-glucose | [18F]FDG | Glucose metabolism | Richards and Scott 2012; Sowa et al. 2018 | Srinivasan et al. 2020 | Koepp et al. 2005 |
| [18F]-Fluoro-L-DOPA | [18F]FDOPA | Dopamine | See Supporting Information, Mossine et al. 2019, 2020 | Kaufhold et al. 2013; Mejia et al. 1991 | Minn et al. 2009 |
| [18F]-Fluoroethoxy- benzovesamicol | [18F]FEOBV | Vesicular acetylcholine transporter | Shao et al. 2011b | Petrou et al. 2014 | Petrou et al. 2014 |
| [18F]-Fluorocholine | [18F]FCH | Choline biochemistry | Rodnick et al. 2013 | DeGrado et al. 2002; Fabbri et al. 2014 | Davenport et al. 2020 |
| [18F]-Flurbiprofen | Amyloid; [18F]AV45 | Amyloid plaques | c | Joshi et al. 2014 | Frey and Koepp 2016 |
Table 1: Radiotracers used clinically at the University of Michigan (Continued)

| Radiotracer                                      | Abbreviation | Application                | Radiosynthesis | Dosimetry                      | Historical Imaging   |
|-------------------------------------------------|--------------|-----------------------------|-----------------|--------------------------------|----------------------|
| [18F]-Fluoro-3′-deoxy-3′-L-fluorothymidine       | [18F]FLT     | Cellular proliferation      | Shao et al. 2011b | Vesselle et al. 2003; Mendes et al. 2018 | Bertagna et al. 2013 |
| [18F]-Flubatine                                  | [18F]FLBT    | αβ2 nACHR                  | Hockley et al. 2013 | Kranz et al. 2016                 | Sattler et al. 2012  |
| [18F]-Flutemetamol                               | Vizamyl, [18F]GE67 | Amyloid plaques         | ; Snellman et al. 2014 | Kooie et al. 2009                 | Frey and Koope 2016  |
| [18F]-Fluoromisonidazole                         | [18F]FMISO   | Tumor hypoxia              | ; Ross et al. 2012 | Graham et al. 1997                | Bruehlmeier et al. 2004 |
| [18F]-Fluropropyl-dihydrotetabenazine            | [18F]FP-TBZ, [18F]AV133 | VMAT2               | Li et al. 2010  | Lin et al. 2010                   | Kilbourn and Koope 2019 |
| [18F]GBR13119 / [18F]GBR12909                   | [18F]GBR     | DAT                        | Haka and Kibboun 1988, 1990 | Kibboun et al. 1989          | Koeppe et al. 1990b  |
| 4-[18F]Fluoro-m-hydroxyphenethylguanidine        | [18F]MHPG    | NET                        | Raffel et al. 2018 | Raffel et al. 2018                | Raffel et al. 2018   |
| 2′-Methoxyphenyl-(N-2′-pyridinyl)-p-[18F]fluoro- benzamidoethylpiperazine | [18F]MPPF | 5-HT1A Receptor          | Shao et al. 2011b | See Supporting Information       | Aznavour and Zimmer 2007 |
| [18F]Sodium Fluoride                            | [18F]NaF     | Bone imaging               | Shao et al. 2011b | Segall et al. 2010; Silveira et al. 2010 | Wong and Piet 2013  |
| [18F]N-Methyl Lansoprazole                      | [18F]NML     | Tau                        | Kramer et al. 2020 | Kramer et al. 2020                | Kramer et al. 2020   |
| 4-[18F]Fluoro-p-hydroxyphenethylguanidine        | [18F]PHPG    | NET                        | Raffel et al. 2018 | Raffel et al. 2018                | Raffel et al. 2018   |
| **Other Radiotracers**                          |              |                             |                 |                                 |                      |
| [13N]Ammonia                                    | [13N]NH3     | Blood flow                 | Scott 2012      | Yi et al. 2015                   | Beanlands et al. 1994 |
| [15O]Water                                      | [15O]H2O     | Blood flow                 | Dick and Watkins 2015 | Brihaye et al. 1995           | Minoshima et al. 1993 |
| [68Ga]DOTATATE                                  | NETSPOT      | Somatostatin receptors     | NETSPOT prescribing information 2016 | Walker et al. 2013       | l; Fallahi et al. 2019 |
| [68Ga]PSMA-HBEDCC                               | [68Ga]PSMA-11 | Prostate specific membrane antigen | See Supporting Information; Rodnick et al. 2020 | Afshar-Oromieh et al. 2016; Sandgren et al. 2019 | Rodnick et al. 2020 |

aHistorical dosimetry data is no longer extant. Biodistribution data are provided to enable estimation of dosimetry; b UM Imaging data not yet published; c Commercially available under an approved (A)NDA; d Commercially available under an IND.
according to current Good Manufacturing Practice (cGMP) using the guidelines outlined in the US Pharmacopeia, (USP < 823> Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses 2020).

Dosimetry
Radiation-absorbed-dose estimates can either be obtained from literature sources or determined using the OLINDA/EXM 1.0 software package (Stabin et al. 2005). Table 1 provides literature sources of dosimetry wherever available. For any radiotracers where literature dosimetry is unavailable, dosimetry is provided in the Supporting Information.

Imaging
Research PET scans have been conducted since the first PET scanner was installed at the University of Michigan (UM) in the 1980s. Historical examples of imaging studies mostly conducted at our Center with the various radiotracers are provided in Table 1, including practical information on both scanning protocols and image kinetic analysis. Injected dose (MBq), mass dose limits (μg) and historical numbers of subjects scanned are provided in Table 2.

Discussion
At the University of Michigan we have a long history of using PET radiotracers in clinical research studies (using both the RDRC and IND mechanisms). Detailed information for 55 such radiotracers is provided in Table 1, including references for radiosyntheses and dosimetry available in the peer-reviewed literature. Synthesis ([11C]butanol, [18F]ASEM, [18F]FDOPA, [68Ga]PSMA-11) and dosimetry ([18F]ASEM, [11C]butanol, [11C]HED, [11C]LY2795050, [11C]MPH, [18F]MPPF, [11C]PMP, [11C]RO-54864) information that has not previously been published is provided in the Supporting Information associated with this article. Pharmacological dose and radioactivity dosing information for the PET drugs is also provided (Table 2), along with historical numbers of administrations to subjects at the University of Michigan PET Center. Rationale for those radiotracers without mass dose limits is provided in the Supporting Information.

As noted above, a study conducted under RDRC oversight cannot exceed 30 subjects without special provisions. The PET drugs corresponding to some of the larger numbers of subjects discussed herein have been used in numerous different RDRC studies over the course of many years (and decades in some instances). In the event any given study exceeded 30 research subjects, the RDRC committee filed a special summary (Form FDA 2915). At the doses specified, no pharmacological or physiological changes were observed after intravenous administration of any of the PET drugs, and the basic science studies were conducted without exceeding any regulatory radiation dose limits. All scans have been reported to the US FDA in the annual RDRC reports required by the agency.

Conclusion
While an IND (or eIND) is the dominant route to FDA approval for first-in-man studies, collection of the requisite data and preparation of the application can be a daunting
| Radiotracer | Injected Dose (MBq) | Mass dose limit | Number of subjects scanned | Clinically detectable pharmacological effects in humans |
|------------|---------------------|-----------------|----------------------------|------------------------------------------------------|
| **[11C]Radiotracers** | | | | |
| [11C]ACE | 740 | None | 475 | No |
| [11C]ACHC | 740 | ≤5000 μg/subject | 2 | No |
| [11C]BMP | 444 | ≤4625 μg/subject | 65 | No |
| [11C]BUT | 555 | ≤125 μg/kg | 0<sup>a</sup> | a |
| [11C]CFN | 555 | ≤0.03 μg/kg | 1492 | No |
| [11C]CHO | 592 | None | 44 | No |
| [11C]DASB | 666 | ≤8 μg/subject | 179 | No |
| [11C]DTBZ | 555 | ≤50 μg/subject | 1823 | No |
| [11C]EPI | 740 | < 9 μg/subject epinephrine & ≤1 μg/subject norepinephrine precursor | 96 | No |
| [11C]FMZ | 370 | ≤50 μg/subject | 668 | No |
| [11C]HED | 666 | ≤50 μg/subject<sup>b</sup> | 643 | No |
| [11C]LY2795050 | 555 | ≤10 μg/subject | 0<sup>c</sup> | c |
| [11C]MET | 444 | None | 129 | No |
| [11C]MTBZ | 580 | ≤10 μg/subject | 6 | No |
| [11C]PHEN | 740–1480 | ≤127 μg/subject<sup>d</sup> | 59 | No |
| [11C]OMAR | 666 | 0.14 μg/kg | 0<sup>e</sup> | e |
| [11C]PALM | 740 | None | 8 | No |
| [11C]PBR28 | 666 | ≤10 μg/subject | 34 | No |
| [11C]PIB | 666 | ≤13 μg/subject | 592 | No |
| [11C]PE2I | 555 | ≤6.3 μg/subject | 1 | No |
| [11C]PHEN | 740 | ≤6800 μg/subject | 29 | No |
| [11C]PK11195 | 888 | ≤420 μg/subject | 118 | No |
| [11C]PMP | 555 | ≤200 μg/subject | 801 | No |
| [11C]RAC | 555 | ≤50 μg/subject | 627 | No |
| [11C]SCOP | 1480 | ≤50 μg/subject | 14 | No |
| [11C]TBZ | 1018 | ≤10 μg/subject | 2 | No |
| [11C]TRB | 1110 | ≤31 μg/subject | 26 | No |
| [11C]WAY-100365 | 555 | ≤15 μg/subject | 51 | No |
| **[18F]Radiotracers** | | | | |
| [18F]AV1451 | 370 | ≤20 μg/subject | 92 | No |
| [18F]AZE | 370 | ≤0.67 μg/subject | 1 | No |
| Auxumin | 370 | ≤20 μg/subject | 228<sup>f</sup> | No |
| [18F]FAZA | 296 | ≤3.5 μg/subject | 14 | No |
| [18F]FDG | 185–296 | None | 6804 | No |
| [18F]FDOPA | 148 | ≤15 μg/subject | 0<sup>f</sup> | g |
| [18F]FDGB | 296 | ≤1.23 μg/subject | 308 | No |
| [18F]FCH | 222 | ≤100 μg/subject | 67 | No |
| Amyvid | 370 | ≤50 μg/subject | 222 | No |
and resource intensive task. Proceeding under approval of a Radioactive Drug Research Committee therefore represents an attractive mechanism for clinical studies of compounds that have (a) already been studied in man and (b) are well characterized in terms of pharmacology and dosimetry. Initiation of a new study for such an established compound is contingent upon access to mass dose and dosimetry data. The data provided herein will streamline future RDRC approval, and facilitate further basic science investigation of 55 PET drugs that target functionally relevant biomarkers in high impact disease states.

**Supplementary Information**
Supplementary information accompanies this paper at https://doi.org/10.1186/s41181-020-00110-z.

**Additional file 1.**

| Abbreviations |
|---------------|
| ANDA: Abbreviated new drug application; Bq: Becquerels; cGMP: Current good manufacturing practice; eIND: Exploratory IND; FDA: Food and Drug Administration; IND: Investigational new drug; NDA: New drug application; PET: Positron emission tomography; QC: Quality control; RDRC: Radioactive drug research committee; USP: United States Pharmacopeia |
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Authors’ contributions

IMJ and PJHS analyzed data and wrote the manuscript. SJL, ARS, JT, XS, MER, LB, MC, SP and AFB conducted radiosyntheses. VER maintains historical PET records and databases. JR is the lead PET technologist who coordinated scheduling and clinical dosing. BGH, BDH, MC and JT provided quality control and/or quality assurance for PET drug manufacture. LEB coordinated RDRC/IRB submissions. DMR calculated dosimetry. KAF, RAK, MRK and PJHS have supervision responsibility. KAF is Chief of Nuclear Medicine and the authorized user physician. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets used in the current paper are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This article does not contain any original studies with human or animal subjects performed by any of the authors.

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All authors gave their consent for publication.

Competing interests

The authors declare no competing financial interests.

Author details

1Department of Radiology, University of Michigan, 2276 Medical Science Bldg I, SPC 5610, Ann Arbor, MI 48109, USA. 2Present Address: Stanford University, Stanford, CA, USA. 3Present Address: Gordon Center for Medical Imaging, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

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References

Afshar-Oromieh A, Hetzheim H, Kübler W, Kratochwil C, Giesel FL, Hope TA, Eder M, Eisenhut M, Kopka K, Haberkorn U. Radiation dosimetry of 68Ga-PSMA-11 (HBED-CC) and preliminary evaluation of optimal imaging timing. Eur J Nucl Med Mol Imaging. 2016;43:1611–20.
Albin R, Koeppke R, Bohren N, Werntzke K, Kilbourn M, Frey K. Spared caudal brainstem SERT binding in early Parkinson disease. J Cereb Blood Flow Metab. 2008;28:441–4.
Albin RL, Koeppke RA, Werntzke K, Zhuang W, Nichols T, Kilbourn MR, Frey KA. Striatal [11C]dihydrotetrabenazine and [11C]methylphenidate binding in Tourette syndrome. Neurology. 2009;72:1390–6.
Alves VH, Abrunhosa AJ, Castelo-Branco M. Optimisation of synthesis, purification and reformulation of (R)-[N-Methyl-11C]PK11195 for in vivo PET imaging studies. In Proceedings of the 2013 IEEE 3rd Portuguese Meeting in Bioengineering (ENBENG), Braga, Portugal, 20–23 February 2013; pp. 1–5.
Aznavour N, Zimmer L. [18F]MPPF as a tool for the in vivo imaging of 5-HT1A receptors in animal and human brain. Neuropsychopharmacology. 2007;52:695–707.
Beanlands RS, Muzik O, Hutchins GD, Wolfe ER Jr, Schwaiger M. Heterogeneity of regional nitrogen 13-labeled ammonia tracer distribution in the normal human heart: comparison with rubidium 82 and copper 62-labeled PTSM. J Nucl Cardiol. 1994;1:225–35.
Beck R, Roep B, Carlsen JM, Huissman MC, Lebsch JA, Andratschke N, Picchio M, Souvatzoglou M, Machulla H-J, Pietr M. Pretreatment 18F-FAZA PET Predicts Success of Hypoxia-Diected Radiochemotherapy Using Tirapazamine. J Nucl Med. 2007;48:973–980.
Bertagna F, Basotto G, Guibbini R. The role of F-18-fluorothymidine PET in oncology. Clin Trans Imaging. 2013;1:77–97.
Blecha JE, Henderson BD, Hockley BG, Van Brocklin HF, Zubieta J-K, DaSilva AF, Kilbourn MR, Koeppke RA, Scott PJH, Shao X. An updated synthesis of [11C]Cafenantil for positron emission tomography (PET) imaging of the μ-opioid receptor J. Labeled Comp Radiopharm. 2017;50:375–80.
Brihaye C, Depresseuc J, Comar D. Radiation dosimetry for bolus administration of oxygen-15-water. J Nucl Med. 1995;36:651–6.
Brown AK, Fujita M, Fujimura Y, Liow J-S, Stabin M, Ryu YH, Imazumi M, Hong J, Pike WW, Innis RB. Radiation dosimetry and biodistribution in monkey and man of 1-13C-PBR28: a PET radioligand to image inflammation. J Nucl Med. 2007;48:2072–9.
Bruehlmeier M, Roelcke U, Schubiger PA, Ametamy SM. Assessment of hypoxia and perfusion in human brain tumors using PET with [18F]-fluoromisonidazole and [15O]H2O. J Nucl Med. 2004;45:1851–9.
DaSilva JN, Carey JE, Sherman PS, Pisani TJ, Kilbourn MR. Characterization of [11C]tetrabenazine as an in vivo radioligand for the vesicular monoamine transporter. Nucl Med Biol. 1994;21:151–6.

DaSilva JN, Kilbourn MR, Mangner TJ. Synthesis of a [11C]tetrabenazine, a vesicular monoamine uptake inhibitor, for PET imaging studies. Appl Radiat Isot. 1993b;44:673–6.

Davenport MS, Montgomery JS, Kunji LP, Siddiqui J, Shankar PR, Rajendiran T, Shao X, Lee E, Denton B, Barnett C, Pier M. 131I–choline PET/impMRI for detection of clinically significant prostate cancer: part 1. Improved risk stratification for MRI-guided transrectal prostate biopsies. J Nucl Med. 2020b;61:337–43.

de Jong HW, Rijzewijk LJ, Lutterink M, van der Meer RW, Lamb HJ, Smits JW, Diamant M, Lammerding AA. Kinetic models for analysing myocardial [18F]fluoromisonidazole data. Eur J Nucl Med Mol Imaging. 2009;36:696–79.

DeGrado TR, Reiman RE, Price DT, Wang S, Coleman RE. Pharmacokinetics and radiation dosimetry of 18F-fluorocholine. J Nucl Med. 2002;43:92–6.

Del Rosario RB, Jung Y-W, Caraher J, Chakravarty PK, Wieland DM. Synthesis and preliminary evaluation of [13C]–(++)-phenylephrine as a functional heart neuronal PET agent. Nucl Med Biol. 1996;23:611–6.

Deloar HM, Fujiwara T, Nakamura T, Itoh M, Imai D, Miyaka M, Watanuki S. Estimation of internal absorbed dose of L-[39C]-dihyrotetrabenazine: a radioligand for studying the vesicular monoamine transporter. Appl Radiat Isot. 1993a;44:1487–9.

Dollé F, Bottlaender M, Dompfel S, Emond P, Faveau C, Coulon C, Ottaviani M, Valette H, Meunier D, Bailly C, Guillemin N. Highly efficient synthesis of [11C]CPE21, a selective radioligand for the quantification of the dopamine transporter using PET. J Labelled Comp Radiopharm. 2000;43:997–1004.

Drazen MJ, Persson LM, Mangner TJ. Synthesis of a [15C]-[13C]tetrabenazine, a vesicular monoamine uptake inhibitor, for PET imaging studies. Appl Radiat Isot. 1993b;44:673–6.

Drake LR, Pham JM, Desmond TJ, Mossine AV, Lee SJ, Kilbourn MR, Koepp RA, Brooks AF, Scott PJH. Identification of AV-1541 as a weak, nonselective inhibitor of monoamine oxidase. ACS Chem Neurosci. 2019;10:3839–46.

Duvernois CS, Raffel DM, Swanson SD, Jaswal M, Mueller G, Ibrahim E-S, Pennathur S, Plunkett C, Stojanovska J, Brown MB, Pop-Busui R. Left ventricular metabolism, function, and sympathetic innervation in men and women with type 1 diabetes. J Nucl Cardiol. 2016;23:960–9.

Fabbri C, Galli G, Bersani S, Mautone V, Bonetti M, Matteucci F. Radiation dosimetry of [18F]fluorocholine PET/CT studies in prostate cancer patients. Phys Med. 2014;30:1243–4.

Fabbri C, Galli G, Bersani S, Mautone V, Sarti G, Strigari L, Benassi M, Matteucci F. Radiation dosimetry of [18F]fluorocholine PET/CT studies in prostate cancer patients. Phys Med. 2014;30:1243–4.

Falalli B, Manati-Farid E, Eftekhari M, Fard-Esfahani A. Diagnostic efficiency of [18F]Ga-DOTATATE PET/CT as compared to [123I]–Octreotide SPECT/CT and conventional morphologic modalities in neuroendocrine tumors. Asia Ocean J Nucl Med Biol. 2019;7:129–40.

FDA Guidance for Industry and Researchers. The Radioactive Drug Research Committee: Human Research without an Investigational New Drug Application. 2010. https://www.fda.gov/media/76286/download. Accessed 7 Jul 2020.

Frey KA, Koepp RA, PET amyloid analyses. J Nucl Med. 2016;57:1168–82.

Frey KA, Koeppe RA. PET amyloid analyses. J Nucl Med. 2016;57:1168

Gao Y, Kellar KJ, Yasuda RP, Tran T, Xiao Y, Dannals RF, Horti AG. Derivatives of dibenzothiophene for PET imaging of a7-nicotinic acetylcholine receptors. J Med Chem. 2013;56:7574–89.

Graham MM, Peterson LM, Link JM, Evans ML, Rasey JS, Koh W-J, Caldwell JH, Krohn KA. Fluorine-18-Fluoromisonidazole radiation dosimetry in imaging studies. J Nucl Med. 1997;38:1631–6.

Hakso MS, Kilbourn MR. Synthesis of [18F]-GBR 13119 as a weak, nonselective inhibitor of monoamine oxidase. Braz Arch Biol Technol. 2007;50:77–90.

Halldin C, Erixon-Lindroth N, Pauli S, Estournel H, Guilloteau D, Maziere B, Crouzel C. Highly efficient synthesis of [11C]PE2I, a selective radioligand for the quantification of the dopamine transporter using PET. J Labelled Comp Radiopharm. 1993:39:279–89.

Harapanhalli RS. Food and Drug Administration requirements for testing and approval of new radiopharmaceuticals. Semin Nucl Med. 2010;40:364–84.

Hirvonen J, Rolvainen A, Vinta J, Heilin S, Näägren K, Rimme JO. Human biodistribution and radiation dosimetry of [11C]-(+)-β-carbolin-1155, the prototypic PET ligand to image inflammation. Eur J Nucl Med Mol Imaging. 2013;37:606–12.

Hockley BG, Stewart MN, Sherman P, Quesada C, Kilbourn MR, Albin RL, Scott P.H. (−)-[18F]fluorodopa: evaluation in rhesus monkeys and a report of the first fully automated radiosynthesis validated for clinical use. J Labelled Comp Radiopharm. 2013;56:595–9.
Joshi AD, Pontecorvo MJ, Adler L, Stabin MG, Skovrinsky DM, Carpenter AP, Mintun MA. Radiation dosimetry of forbetapir F 18. EJNMMI Res. 2014;4(4).

Junck L, Olson JM, Clay BJ, Koeppa RA, Watkins GL, Jewett DM, McKeever PE, Wieland DM, Kilbourn MR, Starosta-Rubinstein SM, Mancini WR, Kuhl DE, Greenberg HS, Young AB. PET imaging of human lizamins with ligands for the peripheral benzodiazepine binding site. Ann Neurol. 1989;26:752–8.

Kuhl DE, Kaope RA, D'Souza M, Sharma R, Mishra AK, Mondal A, Dwarkanath BS. Estimation of patient dose in $^{11}$C-FDG and $^{18}$F-FDOPA PET/CT examinations. J Can Res Ther. 2013;9:477–83.

Kilbourn MR, Carey JE, Koeppa RA, Hala MS, Hutchins GD, Sherman PS, Kuhl DE. Biodistribution, dosimetry, metabolism and monkey PET studies of $^{11}$C-GF 13119. Imaging the dopamine uptake system in vivo. Nucl Med Biol. 1989;16:569–76.

Kilbourn MR, DaSilva JN, Frey KA, Koeppa RA, Kuhl DE. In vivo imaging of vesicular monoamine transporters in human brain using $^{11}$C-Tetrabenazine and positron emission tomography. J Neurochem. 1993;60:2315–8.

Kilbourn MR, Koeppa RA. Classics in neuroimaging: radioligands for the vesicular monoamine transporter 2. ACS Chem Neurosci. 2019;10:25–9.

Koeppa RA, Frey KA, Mulholland GK, Kilbourn MR, Buck A, Lee KS, Kuhl DE. $^{11}$C-Tropinol binds to vesicular transporters in human brain. J Nucl Med. 1994;35:1189–92.

Koeppa RA, Gilman S, Joshi A, Liu S, Little R, Junck L, Heumann M, Frey KA, Albin RL. $^{11}$C-DBT8 and $^{18}$F-FDG PET measures in differentiating dopaminergic. J Nucl Med. 2005;46:936–44.

Koeppa RA, Halin RF, Koeppa RA, Hala MS, Kuhl DE. Compartmental analysis of $^{11}$C-flumazenil kinetics for the estimation of ligand transport rate and receptor distribution using positron emission tomography. J Cereb Blood Flow Metab. 1991;11:735–44.

Koeppa RA, Kilbourn MR, Frey KA, Penney JB, Hala MS, Kuhl DE. Imaging and kinetic modeling of $^{18}$F-GNR 12909, a dopamine uptake inhibitor. J Nucl Med. 1990;31(Suppl):720.

Koeppa RA, Mangner T, Betz AL, Shulkin BL, Allen R, Kollos P, Kuhl DE, Agranoff BW. Evaluation of $^{11}$C-flumazenil binding to translocator protein increases with progression of Alzheimer's disease. Neurobiol Aging. 2016;44:27–39.

Koelle M, Lewis DM, Buckerly C, Neilsen N, Vandenbulcke M, Brooks DJ, Van Laere K. Whole-body biodistribution and radiation dosimetry of $^{11}$C-GBR 12909: a dopamine transporter 1 ligand. J Nucl Med. 2009;50:818–22.

Kraus V, Brooks AF, Haeger A, Kuljs RO, Rafique W, Koeppa RA, Raffel DM, Koeppa RA, Scott PJH, Pes PJ. Evaluation of EJNMMI Physics. 2016;3:25.

Krasnova RN, Andonson J, Truong P, Nag S, Shchukina EV, Hallidin C. A fully automated one-pot synthesis of [carboxy-$^{11}$C]WAY-106635 for clinical PET applications. Appl Radiat Isot. 2009;67:73–8.

Kreis WC, Lyoo CH, Low JS, Wei M, Snow J, Page E, Jenko KJ, Morse OL, Zoghbi SS, Pike W, Turner RS, Inns RR. $^{11}$C-PBR28 binding to translocator protein increases with progression of Alzheimer's disease. Neurobiol Aging. 2016;44:53–61.

Kuhl DE, Koeppa RA, Minoshima S, Snyder SE, Ficaro EP, Foster NL, Frey KA, Kilbourn MR. In vivo mapping of cerebral cholinergic receptors: methodology and kinetic modeling alternatives. J Cereb Blood Flow Metab. 1994;14:885–99.

Kramer V, Brooks AF, Haeger A, Kuljs RO, Rafique W, Koeppa RA, Raffel DM, Koeppa RA, Scott PJH, Pes PJ. Evaluation of $^{11}$C-flumazenil binding to translocator protein increases with progression of Alzheimer’s disease. Neurobiol Aging. 2016;44:27–39.

Kranz M, Bear WB, Sattler B, Tiepot S, Wilke S, Deuther-Donat CK, Fischer S, Patt M, Schildan A, Patt J, Smits R, Hoepfing A, Steinbach J, Sabri O, Brust P. Radiation dosimetry of the $^{11}$C-carboxylic acid derivative with ligand $^{11}$C-flumazenil, comparing preclinical PET/CT and PET/CT to first-in-human PET/CT results. EJNMMI Phys. 2016;3:25.

Krisnikova RN, Andonson J, Truong P, Nag S, Shchukina EV, Hallidin C. A fully automated one-pot synthesis of [carboxy-$^{11}$C]WAY-106635 for clinical PET applications. Appl Radiat Isot. 2009;67:73–8.

Kreis WC, Lyoo CH, Low JS, Wei M, Snow J, Page E, Jenko KJ, Morse OL, Zoghbi SS, Pike W, Turner RS, Inns RR. $^{11}$C-PBR28 binding to translocator protein increases with progression of Alzheimer's disease. Neurobiol Aging. 2016;44:53–61.

Krumm N, Vander Borge TM, Kilbourn MR, Jewett DM, Lee LC, Kuhl DE. Kinetic evaluation of $^{11}$C-flumazenil kinetic analysis and PET drug discovery. J Nucl Med. 1995;36:1189–92.

Koelle M, Lewis DM, Buckerly C, Neilsen N, Vandenbulcke M, Brooks DJ, Van Laere K. Whole-body biodistribution and radiation dosimetry of $^{11}$C-GBR 12909: a dopamine transporter 1 ligand. J Nucl Med. 2009;50:818–22.

Kraus V, Brooks AF, Haeger A, Kuljs RO, Rafique W, Koeppa RA, Raffel DM, Koeppa RA, Scott PJH, Pes PJ. Evaluation of $^{11}$C-flumazenil binding to translocator protein increases with progression of Alzheimer's disease. Neurobiol Aging. 2016;44:27–39.

Koelle M, Lewis DM, Buckerly C, Neilsen N, Vandenbulcke M, Brooks DJ, Van Laere K. Whole-body biodistribution and radiation dosimetry of $^{11}$C-GBR 12909: a dopamine transporter 1 ligand. J Nucl Med. 2009;50:818–22.

Kraus V, Brooks AF, Haeger A, Kuljs RO, Rafique W, Koeppa RA, Raffel DM, Koeppa RA, Scott PJH, Pes PJ. Evaluation of $^{11}$C-flumazenil binding to translocator protein increases with progression of Alzheimer's disease. Neurobiol Aging. 2016;44:27–39.

Kraus V, Brooks AF, Haeger A, Kuljs RO, Rafique W, Koeppa RA, Raffel DM, Koeppa RA, Scott PJH, Pes PJ. Evaluation of $^{11}$C-flumazenil binding to translocator protein increases with progression of Alzheimer's disease. Neurobiol Aging. 2016;44:27–39.

Kraus V, Brooks AF, Haeger A, Kuljs RO, Rafique W, Koeppa RA, Raffel DM, Koeppa RA, Scott PJH, Pes PJ. Evaluation of $^{11}$C-flumazenil binding to translocator protein increases with progression of Alzheimer's disease. Neurobiol Aging. 2016;44:27–39.

Kraus V, Brooks AF, Haeger A, Kuljs RO, Rafique W, Koeppa RA, Raffel DM, Koeppa RA, Scott PJH, Pes PJ. Evaluation of $^{11}$C-flumazenil binding to translocator protein increases with progression of Alzheimer's disease. Neurobiol Aging. 2016;44:27–39.

Kraus V, Brooks AF, Haeger A, Kuljs RO, Rafique W, Koeppa RA, Raffel DM, Koeppa RA, Scott PJH, Pes PJ. Evaluation of $^{11}$C-flumazenil binding to translocator protein increases with progression of Alzheimer's disease. Neurobiol Aging. 2016;44:27–39.
Mossessian, M. Duarte-Vogel, SM, Stout, DB, Roos, KP, Lawson, GW, Jordan, MC, Ogden, A, Matter, C, Sadeghi, S, Mills, GQ, Schelbert, HR, Rudu, CG, Czemins, J, Couto, M, Phelps, ME. INDs for PET molecular imaging probes/approach by an academic institution. Mol Imaging Biol. 2014;16(1):441–8.

Mossine, AV, Brooks, AF, Henderson, BD, Hockley, BG, Frey, KA, Scott, PJH. An updated radiosynthesis of (18F)AV1451 for Tau PET imaging. EJNMMI Radiopharm Chem. 2017;2:7.

Mossine, AV, Tansey, SS, Brooks, AF, Makaravage, KJ, Nekissi, N, Miller, JM, Henderson, BD, Skaddan, M, Sanforn, MS, Scott, PJH. One-pot synthesis of high molar activity (6-18F)Fluoro-L-DOPA by cu-mediated fluorination of a BPin precursor org. Biomol Chem. 2017;17:8701–5.

Mossine, AV, Tansey, SS, Brooks, AF, Makaravage, KJ, Nekissi, N, Miller, JM, Henderson, BD, Skaddan, M, Sanforn, MS, Scott, PJH. Synthesis of high molar activity (6-18F)fluoro-L-DOPA suitable for human use by cu-mediated fluorination of a BPin precursor. Nat Protoc. 2020;15:1742–59.

Mulholland, GK, Jeffs, DW, Toorongian, SA. Routine synthesis of N-[11C]-methoxy-2-propamine by photolytic mediated reduction with [11C]Formaldehyde. Appl Radiat Isot. 1989;39:373–9.

Mulholland, GK, Kilbourn, MR, Sherman, P, Carey, J, Frey, KA, Koepp, RA, Kuhl, DE. Synthesis, in vivo biodistribution and dosimetry of [11C]-Methylpiperidyl Benzilate (11C)JNMB), a muscarinic acetylcholine receptor antagonist. Nucl Med Biol. 1995;22:13–7.

Mulholland, GK, Otto, CA, Jewett, DM, Kilbourn, MR, Koepp, RA, Sherman, PS, Petry, NA, Carey, J, Atkinson, ER, Archer, S, Frey, KA, Kuhl, DE. Synthesis, rodent biodistribution, dosimetry, metabolism, and monkey images of carbon-11-labeled (11C)-Tropenzil Benzilate: a central muscarinic receptor imaging agent. J Nucl Med. 1992;33:423–30.

Mund, G, Nguyen, TQ, Zhang, Z, Zwick, M, Chakraborty, P, Wieland, DM, Schweiger, M. Evaluation of sympathetic nerve terminals with [11C]Clepinephrine and (18F)Hydroxyephedrine and positron emission tomography. Circulation. 2000;101:156–23.

Murphy, R, Harris, P, Simpson, N, Van Heerum, R, Leibell, R, Mann, JJ, Parsey, R. Whole body (11C)-dihydroetremabazine imaging of baboons: biodistribution and human radiation dosimetry estimates. Eur J Nucl Med Mol Imaging. 2008;35:790–7.

Nagayama, M, Zheng, M-Q, Henry, S, Nabil, N, Lin, S-F, Ropchan, J, Labaree, D, Najafzadeh, S, Kapinos, M, Tausher, J. Neumeister, A, Carson, RE, Huang, Y. Test-retest reproducibility of binding parameters in humans with [11C]LY279520. An antagonist PET radiotracer for the kappa opioid receptor. J Nucl Med. 2015;56:243–8.

NETSPOT Prescribing Information. 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208547s000lbl.pdf. Accessed 7 Jul 2020.

Newberg, AB, Ray, R, Scheuermann, J, Wintering, N, Saffer, J, Schmitz, R, Freifelder, R, Karp, J, Lerman, C, Divgi, C. Dosimetry of 11C-

O’Keefe, GJ, Sauberth, NG, S, Ackerman, T, Tochon-Danguy, HJ, Chan, JC, Gong, S, Dyrs, T, Lindemann, S, Holl, G, Dinkelborg, L. Vilmagne, R, Rowe CC. Radiation dosimetry of a bromo-aryl tracers 11C-PiB and 18F-BAY94-9172. J Nucl Med. 2009;50:309–15.

Parsey, R, Belanger, MJ, Sullivan, GM, Simpson, NR, Stabin, MG, Van Heerum, R, Mann, JJ. Biodistribution and radiation dosimetry of 11C-WA110,635 in humans. J Nucl Med. 2005;46:614–9.

Petru, M, Frey, KA, Kilbourn, MR, Scott, PJH, Raffel, D, Albin, RL, Koepp, RA. In vivo imaging of human cholinergic nerve terminals with (–)-5-18F-Fluorooxybenzovesamicol: biodistribution, dosimetry, and tracer kinetic analyses. J Nucl Med. 2014;55:396–404.

Pietr, M, Park, H, Khan, A, Siddiqui, J, Hussain, H, Chenevert, T, Wood, D, Johnson, T, Shah, RB, Meyer, C. Detection of aggressive primary prostate cancer with 11C-choline PET/CT using multimodality fusion techniques. J Nucl Med. 2009;50:1588–93.

Pietr, M, Shao, X, Raffel, DM, Davenport, M, Montgomery, J, Kunju, P, Hockley, BG, Siddiqui, J, Scott, PJH, Chinnayani, A, Rajendiran, T. Preclinical evaluation of T1C-Sarcosine as a substrate of proton-coupled amino acid transporters and first human application in prostate cancer. J Nucl Med. 2017;58:1216–23.

Quarles, RP, Minturn, MA, Larkow, K, Markham, J, MacLeod, AM, Raichle, ME. Measurement of regional cerebral blood flow with positron emission tomography: a comparison of [133Xe]oxygen to [133Xe]Boranol with distributed-parameter and compartmental models. J Cerebral Blood Flow Metab. 1993;13:733–47.

Raffel, DM, Corbett, JR, Del Rosario, RB, Gidney, SL, Chiao, P-C, Schweiger, M, Wieland, DM. Synthesis of carbon-11-phenylphosphate: an Mo-sensitive marker of cardiac sympathetic neurons. J Nucl Med. 1996;37:1923–31.

Raffel, DM, Jung, Y-W, Koepp, RA, Jiang, KS, Gu, G, Scott, PJH, Murthy, V, Rothley, J, Frey, KA. First-in-human studies of [18F]Fluoromisonidazole (1-(2-Hydroxy-3-piperidyl)-N-(2-tosylmethyl)-1H-indole-1-carboxamide) in healthy volunteers: preliminary results. Nucl Med Biol. 2012;39:203–8.

Riss, PJ, Ferrari, V, Bielik, R, Canales-Candela, R, Smith, R, Aigbirhio, FI. Synthesis of [18F]Fluoromisonidazole (1-(2-Hydroxy-3-piperidyl)-N-(2-tosylmethyl)-1H-indole-1-carboxamide) in healthy volunteers. Nucl Med Biol. 2011;38:413–20.
Sandgren K, Johansson L, Axelsson J, Jonsson J, Ögren M, Ögren M, Andersson M, Strandberg S, Nyholm T, Riklund K, Widmark A. Radiation dosimetry of \textsuperscript{68}GaPSMA-11 in low-risk prostate cancer patients. J Nucl Med. 2019;62.

Sattler B, Kranz M, Patt M, Donat C, Deucher-Conrad W, Hoepping A, Sattler T, Steinbach J, Brust P, Sabri O. Incorporation dosimetry of F-18-Fibatine - comparison of animal model data with first-in-man results. J Nucl Med. 2012;53(suppl):1503.

Savi A, Incerti E, Fallanca F, Bettinardi V, Rosseti F, Montierni C, Complierecchio A, Negri G, Zannini P, Gionoli L, Piccio F. First evaluation of PET-based human biodistribution and dosimetry of \textsuperscript{18}F-FAZA, a tracer for imaging tumor hypoxia. J Nucl Med. 2017;58:1234–9.

Schwarz SW, Decristoforo C, US and EU radiopharmaceutical diagnostic and therapeutic nonclinical study requirements for clinical trials authorizations and marketing authorizations. EJNMMP Radiopharm Chem. 2019;410.

Schwarz SW, Decristoforo C, Goodbody AE, Singhal N, Saliba S, Ruddy PS, Zukotynski K, Ross AA. Harmonization of US, European Union, and Canadian first-in-human regulatory requirements for radiopharmaceuticals: is this possible? J Nucl Med. 2019;60:158–66.

Schwarz SW, Dick D, VanBrocklin HF, Hoffmann JM. Regulatory requirements for PET drug production. J Nucl Med. 2014;55:1132–7.

Scott DJ, Heitzeg MM, Koepe RA, Stohler CS, Zubieta J-K. Variations in the human pain experience mediated by ventral and dorsal basal ganglia dopamine activity. J Neurosci. 2006;26:10789–95.

Scott P.H. Synthesis of \textsuperscript{15}N-Ammonia. In: Hockley BG, Scott P.JH, editors. Radiochemical syntheses volume 1: radiotherapeutics for positron emission tomography. vol. 31. Chichester: Wiley; 2012. p. 315–20.

Segall G, Delbeke D, Stabon MG, Even-Sapir E, Fair J, Sajdak R, Smith GT. SNM practice guideline for sodium \textsuperscript{18}F-fluoride PET/\textsuperscript{18}FDG bone scans 1.0. J Nucl Med. 2010;51:1813–20.

Selzer MA, Jahan SA, Sparks R, Stout DB, Satyamurthy N, Dahlborn M, Phelps ME, Barrior JR. Radiation dose estimates in humans for \textsuperscript{14}C-acetate whole-body PET. J Nucl Med. 2004;45:1233–6.

Shao X, Fawaz MV, Jang K, Scott P.H. Ethanolic carbon-11 chemistry: the introduction of green radiochemistry. Appl Radiat Isot. 2014;84:125–9.

Shao X, Hoareau R, Hockley BG, Tluczek LJ, Henderson BD, Padgett HC, Scott P.JHSA. Highlighting the versatility of the Tracerlab synthesis modules. Part 1: fully automated production of \textsuperscript{18}F-labelled radiotherapeutics using a Tracerlab FXn. J Labelled Comp Radiopharm. 2011b;54:292–307.

Shao X, Hoareau R, Runke AC, Tluczek LJM, Hockley BG, Henderson BD, Scott P.H. Highlighting versatility of the Tracerlab synthesis modules. Part 2: fully automated production of \textsuperscript{18}F-labelled radiotherapeutics using a Tracerlab FXn. J Labelled Comp Radiopharm. 2011a;54:819–38.

Shao X, Jang K, Scott P.H. Synthesis of 1-(2,4-Dichlorophenyl)-4-cyano-5-(4-\textsuperscript{18}F-methoxyphenyl)-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide (\textsuperscript{18}F-CQMAR). In: Scott P.H, editor. Radiochemical syntheses volume 2: further radiopharmaceuticals for positron emission tomography and new strategies for their production. Hoboken: Wiley; 2015. p. 73–80.

Silveira MB, Soares MA, Valente ES, Waquil SS, Ferreira AV, dos Santost RG, da Silva JB. Synthesis, quality control and dosimetry of the radiopharmaceutical \textsuperscript{18}F-sodium fluoride produced at the Center for Development of Nuclear Technology – CDTN. Braz J Pharm Sci. 2010;46:563–9.

Snellman A, Gunupudi N, Sherman PS, Butch ER, Skaddan MB, Koeppe RA, Kuhl DE. Radiolabeled cholinesterase substrates: in vitro methods for determining structure-activity relationships and identification of a positron emission tomography radiopharmaceutical for in vivo measurement of butyrylcholinesterase activity. J Cereb Blood Flow Metab. 2001;21:1322–43.

Songmen S, Nepal P, Olasvödy T, Sapare J. Axumin positron emission tomography: novel agent for prostate cancer biochemical recurrence. J Clin Imaging Sci. 2019;49.

Söörenen J, Dwowski R, Lax M, Johansson S. Regional distribution and kinetics of \textsuperscript{18}F-fluciclovine (anti-[\textsuperscript{18}F]FACBC), a tracer of amino acid transport, in subjects with primary prostate cancer. Eur J Nucl Med Mol Imaging. 2013;40:394–402.

Sowa AR, Jackson IM, Desmond TJ, Alicea J, Mufarreh AJ, Pham JM, Stauff J, Winton WP, Fawaz MV, Henderson BD, Hockley BG, Rogers VE, Koepe RA, Scott P.H. Futureproofing \textsuperscript{18}F-fluorodeoxyglucose manufacture at an Academic Medical Center. EJNMMP Radiopharm Chem. 2018;3:12.

Srinivasan S, Chandali JP, Gajwani P, Sgouros G, Mena E, Lodge MA, Wahl RL. Human radiation dosimetry for orally and intravenously administered \textsuperscript{18}F-FDG. J Nucl Med. 2020;61:613–9.

Stabin MG, Sparks RB, Crowe E. The second-generation personal computer software for internal dose assessment in nuclear medicine. J Nucl Med. 2005;46:1023–7.

Suleiman OH, Fejka R, Houn F, Walsh M. The radioactive drug research committee: background and retrospective study of reported research data. J Nucl Med. 2006;47:1220–6.

Tolvanen T, Yi-Heikerta T, Uujja T, Autio A, Lehtokienen P, Minn H, Roivainen A. Biodistribution and radiation dosimetry of \textsuperscript{9}F-MBZ in comparison between rat and human data. Eur J Nucl Med Mol Imaging. 2010;37:874–83.

USP <823> Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses. Radiopharmaceuticals for positron emission tomography. In: USP 43-NF 38. Rockville: The United States Pharmacopeia Convention; 2020.

VanBrocklin HF. Radiopharmaceuticals for drug development: United States regulatory perspective. Curr Radiopharm. 2008;1:2–5.

Vander Borght TM, Kilbourn MR, Koepe RA, DaSilva JN, Carey JE, Kuhl DE, Rattner AJ. In vivo imaging of the brain vesicular amino acid transporters, in subjects with primary prostate cancer. Eur J Nucl Med Mol Imaging. 2013;40:394–402.

Vessel H, Giessner J, Peterson LM, Muzi M, Mankoff DA, Krohn KA. \textsuperscript{18}F-Fluorothymidine radiation dosimetry in human PET imaging studies. J Nucl Med. 2003;44:1482–43.

Virta JR, Tolvanen T, Nägren K, Brück A, Roivainen A, Rinne JD. \textsuperscript{11}C-Methyl-4-piperidinyl-N-butylate radiation dosimetry in humans by dynamic organ-specific evaluation. J Nucl Med. 2008;49:347–53.

Wagner P, US EPA. Inert Reassessment – n-Butanol, CAS #: 71–36-3 and Isobutyl Alcohol, CAS #: 78–83–1. 2005; https://www.epa.gov/sites/production/files/2015-04/documents/butanol.pdf. Accessed 7 Jul 2020.

Walker RI, Smith GT, Liu E, Moore B, Clanton J, Stabin M. Measured human dosimetry of \textsuperscript{68}Ga-DOTATATE. J Nucl Med. 2013;54:855–60.
Washburn LC, Sun TT, Byrd BL, Rafter JJ, Hayes RL, Frey KA, Agranoff BW. 11C-ACHC, a potential agent for positron tomographic measurement of brain amino acid transport. In: Raynaud C, editor. Nuclear medicine and biology: proceedings of the third world congress of nuclear medicine and biology, August 29–September 2, 1982, Paris, France. Paris: Pergamon Press; 1982. p. 642–5.

Wong DF, Kuwabara H, Horti AG, Raymont V, Brasic J, Guevara M, Ye W, Dannals RF, Ravett HT, Nandi A, Rahimim A, Ming JE, Grachev I, Roy C, Cascella N. Quantification of cerebral cannabinoid receptors subtype 1 (CB1) in healthy subjects and schizophrenia by the novel PET radioligand [11C]OMAR. Neuroimage. 2010;52:1505–13.

Wong DF, Kuwabara H, Pomper M, Holt DP, Brasic JR, George N, Frolov B, Willis W, Gao Y, Valentine H, Nandi A, Gapasin L, Dannals RF, Horti AG. Human brain imaging of α7 nACHR with [18F]ASEM: a new PET radiotracer for neuropsychiatry and determination of drug occupancy. Mol Imaging Biol. 2014;16:730–8.

Wong KK, Piert M. Dynamic bone imaging with 99mTc-labeled Diphosphonates and 18F-NaF: mechanisms and applications. J Nucl Med. 2013;54:590–9.

Wrobel MC, Carey JE, Sherman PS, Kilbourn MR. Simplifying the dosimetry of carbon-11-labeled radiopharmaceuticals. J Nucl Med. 1997;38:654–60.

Yang L, Brooks AF, Makaravage KJ, Zhang H, Sanford MS, Scott PJH, Shao X. Radiosynthesis of [11C]Y2795050 for preclinical and clinical PET imaging using cu(II)-mediated Cyanation. ACS Med Chem Lett. 2018;9:1274–9.

Yi C, Yu D, Shi X, He Q, Zhang X, Zhang X. Biodistribution and estimation of radiation-absorbed doses in humans for 11N-ammonia PET. Ann Nucl Med. 2015;29:810–5.

Yoshida T, Kuwabara Y, Ichiyi Y, Sasaki M, Fukumura T, Ichimiya A, Takita M, Ogomori K, Masuda K. Cerebral muscarinic acetylcholinergic receptor measurement in Alzheimer’s disease patients on 11C-N-methyl-4-piperidyl benzilate — comparison with cerebral blood flow and cerebral glucose metabolism. Ann Neurol. 1998;12:35–42.

Zubieta JK, Greenwald MK, Lombardi U, Woods SH, Kilbourn MR, Jewett DM, Koeppke RA, Schuster CR, Johanson CE. Buprenorphine-induced changes in mu-opioid receptor availability in male heroin-dependent volunteers: a preliminary study. Neuropsychopharmacology. 2000;23:326–34.

Zubieta JK, Koeppke RA, Frey KA, Kilbourn MR, Mangner TJ, Foster NL, Kuhl DE. Assessment of muscarinic receptor concentrations in aging and Alzheimer disease with [11C]NMPB and PET. Synapse. 2001;39:275–87.

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