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SNMMI Clinical Trials Network Research Series for Technologists: Clinical Research Primer—Use of Imaging Agents in Therapeutic Drug Development and Approval

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Abstract

The process of bringing a new drug to market is complex and has recently necessitated a new drug discovery paradigm for the pharmaceutical industry that is both more efficient and more economical. Key to this has been the increasing use of nuclear medicine and molecular imaging to support drug discovery efforts by answering critical questions on the pathway for development and approval of a new therapeutic drug. Some of these questions include: (i) Does the new drug reach its intended target in the body at sufficient levels to effectively treat or diagnose disease without unacceptable toxicity? (ii) How is the drug absorbed, metabolized, and excreted? (iii) What is the effective dose in humans? To conduct the appropriate imaging studies to answer such questions, pharmaceutical companies are increasingly partnering with molecular imaging departments. Nuclear medicine technologists are critical to this process as they perform scans to collect the qualitative and quantitative imaging data used to measure study endpoints. This article describes preclinical and clinical research trials and provides an overview of the different ways that radiopharmaceuticals are used to answer critical questions during therapeutic drug development.

Keywords: clinical research, nuclear medicine, PET and SPECT, drug development, clinical trials.

INTRODUCTION

For pharmaceutical companies, the process of discovering a new diagnostic or therapeutic drug and developing it for market is enormously complex (Figure 1), and includes preclinical testing, investigational new drug (IND) applications, clinical trials, new drug applications (NDA), marketing approval from the U. S. Food and Drug Administration (FDA), and post-marketing studies. The goal is to bring safe and effective drugs to market as quickly as possible, but it can take up to 10 years to complete this drug development process, and the lifetime of a US patent (during which pharmaceutical companies need to complete drug discovery/translation/approval, establish the drugs market share, recoup research investment, and turn a profit) is only 20 years. Recent studies estimate the average cost of therapeutic drug development at $1.3 billion per drug, but it can be as high as $5.5 billion (*1,2*). This challenge is further exacerbated when promising drug candidates fail to meet prespecified endpoints in later stage clinical trials after many years of expensive investment. Reimbursement from the Centers for Medicare and Medicaid Services as well as other insurance carriers also go through a review process.

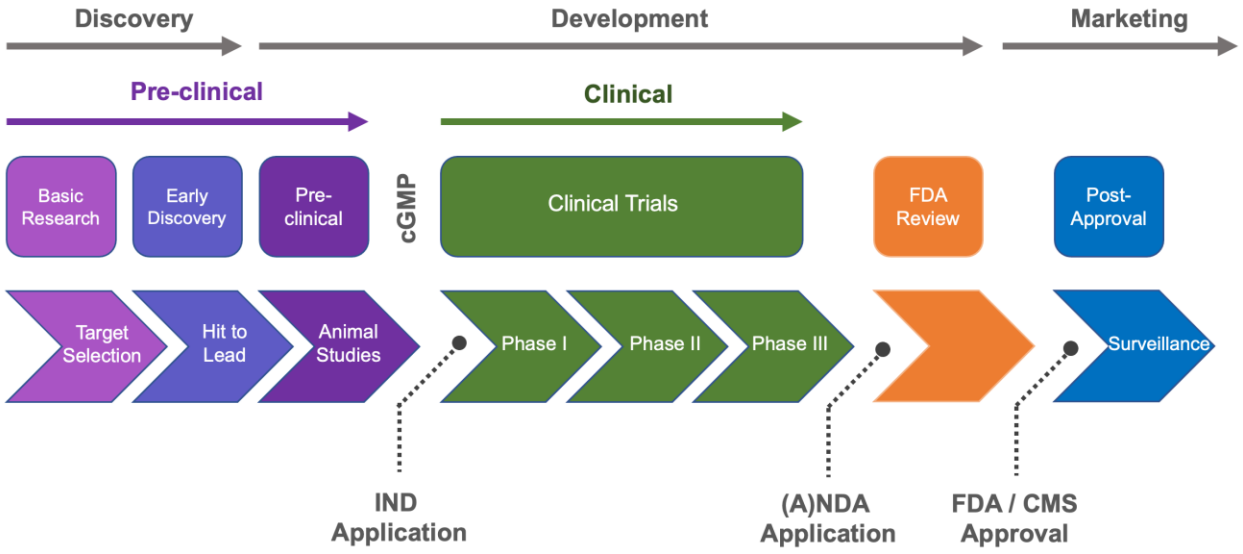

Figure 1: Drug development process

These challenges have necessitated a new drug development paradigm for the pharmaceutical industry that is both more efficient and more economical and, as a result, new technologies are

being used to reduce both the costs and risks associated with drug development. Molecular imaging and nuclear medicine are tools that play a key role in modern drug development owing to their ability to address important questions at each step of the drug discovery process (*2, 3*). For example, imaging studies costing a few tens to hundreds of thousands of dollars enable companies to reduce risk and more confidently make key go/no-go decisions about advancing drugs to clinical studies costing millions to billions of dollars (depending upon size and scope). Such imaging studies require access to different radiopharmaceuticals (e.g., established radiotracers, new radiotracers, radiolabeled drug candidates) and can consist of both preclinical and clinical imaging studies. For example, early drug discovery efforts involve preclinical studies (e.g., *in vitro* autoradiography, *in vivo* animal imaging, *ex vivo* biodistribution), while later drug development trials pivot to clinical studies in human subject volunteers (Phase I, II and III clinical trials conducted under approved Investigational New Drug Applications [INDs]). Upon completion of Phase III studies an NDA can be filed and, once approved, give the sponsor marketing authorization for the drug. Post-marketing Phase IV trials may be required by FDA for long term surveillance of drug safety and efficacy.

In this primer, we describe regulatory and logistical considerations for nuclear medicine departments to participate in preclinical and clinical research, as well as an overview of the different ways that radiopharmaceuticals can be used to answer critical questions pertaining to therapeutic drug development (*2,3*). This paper is a companion to other articles in this series published to date (*4*).

TYPES OF IMAGING STUDIES CONDUCTED DURING DRUG DEVELOPMENT PROCESS

Nuclear medicine imaging (with positron emission tomography (PET) and single photon emission computed tomography (SPECT)) enables industry and academic teams to answer questions central to new drug development. PET and SPECT are increasingly employed during both pre-clinical in vitro (cells) and in vivo (animal models) studies and clinical trials (human research subjects), including:

- Does a drug reach the tissue of interest in pharmacologically active concentrations?
- Does the drug go anywhere else in the body that could cause unwanted side effects?
- Does the molecule engage with the target (e.g., receptor, protein) of interest?
- What is the quantitative relationship between the extent of the drug's interaction with the target and the dose administered to a patient (e.g., receptor occupancy)?
- Can the pharmacological effects of a therapeutic dose be determined using an imaging biomarker (e.g., tumor shrinkage, FDG metabolism/uptake etc. (*3*)), and how long do they persist?

The answers to these questions are critical to translating a drug to initial clinical trials, as well as advancing the drug through clinical trials (phases I – III), and imaging offers a powerful means for drug discovery teams to address such questions.

The questions concerning the distribution and target engagement of a drug can often be answered by labeling a drug molecule itself. For example, radiolabeling of a drug with a PET radionuclide, such as ^{11}C, can be accomplished without altering the properties of the drug. Since it is estimated that ~ 20% of prescribed drugs and ~30% of leading blockbuster drugs contain a fluorine atom (*5*), in such cases the same can also be accomplished with fluorine-18 (*6*). The labeled drug can then be used in preclinical and clinical biodistribution studies (as described further below).

PET imaging can also be used to quantify the pharmacological effects of a therapeutic dose. Such imaging capitalizes on the concept of biological markers (*biomarkers)*. A biomarker is an objective measurement that is an indicator of a biological process happening in a patient and can serve as an indicator for their health. Classical biomarkers are based on laboratory tests (e.g., blood, urine, tissue biopsy), while an imaging biomarker is a measurement of a biological process, for example quantification of amyloid burden using amyloid PET. Frequently, these types of studies might use companion PET radiotracers rather than a radiolabeled drug. Prior to commencing such studies,

it is necessary to confirm that a radiotracer is appropriate for that purpose. When validating a PET tracer, a test-retest experiment is usually conducted to measure repeatability of the measurements and determine within-subject variability (*7*). The test-retest is particularly important if a PET radiotracer is to be utilized in studies involving multiple measurements on the same subject (e.g., receptor occupancy, before and after a therapeutic intervention).

If an imaging biomarker exists for a given condition, then it can be used to diagnose disease and both predict and monitor patient response to experimental new therapeutics in clinical trials. Extending the latter concept further, imaging biomarkers can also be used as a surrogate endpoint in a clinical trial. A surrogate endpoint is defined by FDA as "*a clinical trial endpoint used as a substitute for a direct measure of how a patient feels, functions, or survives"* (*8*). They are recognized by the agency and have been widely used in the drug approval and licensure process (*8,9*). The main difference between an imaging biomarker and a surrogate endpoint is the level of validation. For an imaging biomarker to function as a surrogate endpoint, there must be clinical trials demonstrating the relationship between the imaging biomarker and the true clinical endpoint. Imaging biomarkers have been reviewed (*10*) and, in the case of cancer trials, an imaging biomarker roadmap has been established (*11*). Examples of imaging biomarkers used as surrogate endpoints include amyloid imaging (*12*), assessment of tumor response (*13,14,15*), and [^{11}C]raclopride PET for antipsychotic efficacy (*16*,*17*).

REGULATORY CONSIDERATIONS

Use of nuclear medicine imaging techniques to support drug development involves both preclinical and clinical studies. Such work must be conducted in compliance with applicable institutional, state, and federal regulations governing the use of radioactive material, as well as the rules and regulations describing responsible and ethical conduct in animal and human research. These various regulatory requirements are summarized briefly below, and are covered in detail in other articles in this series (*4*).

Radioactive materials need to be handled under the auspices of approved radioactive materials licenses granted by the Nuclear Regulatory Commission (NRC), or the local state government for agreement states. Such work must also be carried out according to the ALARA (As Low as Reasonably Achievable) principles, which involves making every reasonable effort to ensure worker exposures to ionizing radiation are as low as practical.

In the United States, positron emission tomography (PET) radiopharmaceuticals are prepared according to the principles of current Good Manufacturing Practice (cGMP) outlined in the US Pharmacopeia Chapter <823> (*18*) or Chapter <825> (*19)*), and 21 CFR Part 212 (*20*)). Other radiopharmaceuticals (e.g., radiotherapeutics) are often prepared according to requirements outlined in 21 CFR Parts 210 (*21*) and Part 211 (*22*). The cGMP regulations cover types of facilities, cleanliness and maintenance of the facilities, laboratory controls, equipment, personnel, training, quality assurance, documentation about materials and processes, drug product controls, packaging and labeling requirements, complaint handling and record keeping.

Preclinical (animal) studies need to be conducted under the purview of an Institutional Animal Care and Use Committee and it is typical for pharmaceutical companies to also require collaborating sites to hold Association for Assessment and Accreditation of Laboratory Animal Care International certification. The use of animals to advance medicine and science when there are no non-animal alternatives remains a critical part of drug development, and preclinical work should be conducted in accord with the highest scientific, humane, and ethical principles as laid out in the *Guide for the Care and Use of Laboratory Animals* (*23*).

Clinical studies can only be conducted following both FDA (e.g. Radioactive Drug Research Committee - RDRC or IND application) and institutional (e.g. Institutional Review Board) approval. Regulations for using radiopharmaceuticals under RDRC approval are described in 21CFR361, while the requirements for conducting research under an IND are laid out in 21CFR312. For a detailed description, refer to a companion article in this series (*4*).

TYPES OF RESEARCH STUDIES

Preclinical Studies

While nuclear medicine technologists predominantly work in clinical PET imaging, some may find themselves working in academic PET Centers or pharmaceutical companies. In the latter instances, they will likely find themselves involved in preclinical studies. Preclinical studies are intended to answer many of the same questions that will ultimately be investigated clinically, but earlier in the discovery process and often to make go/no-go decisions about costly clinical translation. There are four main types of preclinical protocols: i) cell studies, ii) autoradiography experiments with post-mortem tissue samples (*in vitro* or *ex vivo*), iii) *in vivo* PET (or SPECT) imaging studies in living animals, and iv) *ex vivo* biodistribution studies in which animals are sacrificed after injection of the tracer, dissected and their organs counted in a gamma counter to establish biodistribution and dosimetry of the tracer.

Cell studies

Cell uptake studies evaluate uptake of a new radiotracer in a cell expressing the drug target of interest. These studies are an economic starting point as they cost considerably less than animal studies. Cell uptake studies offer a preliminary indication of target engagement for a new radiotracer, and also help researchers decide promising ones to advance to animal studies.

Binding affinity experiments

Binding studies quantify the binding characteristics of a new radiopharmaceutical, such as affinity for its target, which is expressed as the dissociation constant (K_D). Lower K_D values correspond to higher affinity molecules. Such studies can be conducted using tissue pellets or autoradiography (see below).

Autoradiography experiments

Autoradiography (ARG) is a technique in which radiolabeled molecules tissues are incubated with radiotracer (*24*), and then exposed to photographic film or phosphor imaging plates to visualize location of radiolabeled molecules. *In vitro* ARG studies utilize post-mortem animal or human tissue samples (e.g., a histologic slice of brain or tumor) that have been previously harvested. The radiolabeled molecule is incubated with post-mortem tissue samples, giving the molecule time to bind to its target (e.g. receptor, protein). The samples are then washed and exposed to film or plates. Note, *in vitro* ARG does not account for the *in vivo* environment (e.g. metabolism). If the latter is needed, then *ex vivo* ARG studies can be undertaken. The radiotracer is first administered intravenously and after some timepoint, animals are sacrificed (with our without *in vivo* PET imaging first, see below) and organs and tissues of interest are harvested for ARG. The post-mortem tissue samples are washed and exposed to film or plates analogous to *in vitro* ARG.

Autoradiography has been used to quantify and localize drugs in organs, tissues and cells for decades. The data can be used to determine K_D for a radiotracer, and target engagement of a therapeutic drug can be confirmed by observing a reduction in signal of the specific radiotracer in the presence of a therapeutic dose (either dosed to the animal (*ex vivo* ARG) or added to the incubation solution (*in vitro* ARG)). Alternatively, the technique can be combined with immunohistochemistry on an adjacent slice of tissue, and observing co-localization of the ARG signal with the fluorescence of target-specific antibodies. Such data sets are critical in validating a new radiotracer and making the decision to advance to preclinical and eventual clinical *in vivo* imaging studies.

In vivo PET (or SPECT) imaging studies

In vivo imaging study logistics closely resemble human studies in that doses, imaging protocols, timing, *i.v*. catheter placement, interventions, attenuation correction, reconstruction and radiation safety all have to be accounted for and planned in the same way. An additional

consideration with animal work is that, unlike human subjects, animals need to be anesthetized for the duration of the study. Depending upon the mechanism of action of a drug, choice of anesthesia can affect the PET data and may need to be accounted for in study design (*25*). For preclinical PET imaging, small mice typically receive ≤9.25 MBq of radiotracer, while larger animals receive higher doses depending on weight (e.g. rodents receive ≤37 MBq, primates receive ≤185 MBq). PET scans can be dynamic, and typical scan lengths are 60 min for a ^{11}C-labeled tracer, or up to 120 min for a ^{18}F-labeled tracer. Static scans, which could be 5 – 20 min in length, can also be acquired at one or more time points after administration of the radiotracer. Baseline scans will give pharmacokinetic and distribution information on a given tracer or labeled drug candidate, while intervention studies (e.g. with a dose of therapeutic) can be used to answer questions about specific biding, target engagement, receptor occupancy at a given dose, etc. In some studies the animal may be sacrificed immediately after the imaging study and organs harvested for further evaluation using autoradiography (see above). Figure 2 (left) shows a baseline nonhuman primate PET scan obtained with [^{1F}F]AH114726, a new radiotracer targeting the $GABA_A$ receptor (*26*). The baseline scan reveals high uptake in the cortical region, which is known to have high expression of $GABA_A$ receptors. To confirm selectivity of the new compound for the target, the scan was repeated in the presence of 1 mg/kg flumazenil, a known selective $GABA_A$ receptor antagonist. The scan confirmed target engagement and selectivity of AH114726 as complete displacement of the radiotracer was apparent upon dosing with flumazenil (Figure 2 right).

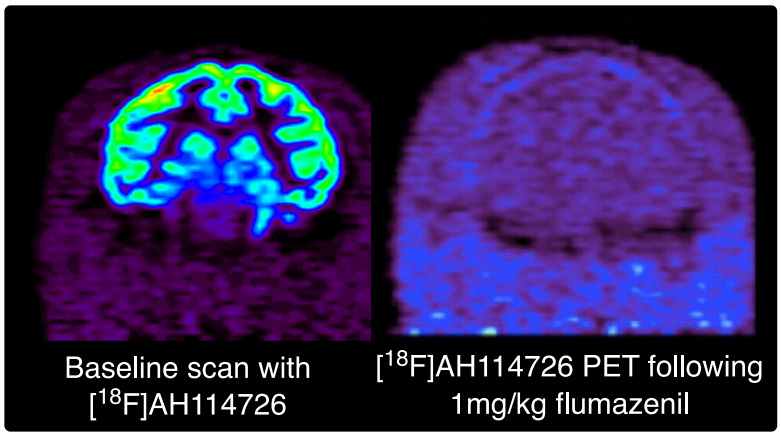

Figure 2: Representative coronal microPET images of control animal imaged with [^{18}F]AH114726 (left), and after displacement with 1 mg/kg flumazenil (right). Reprinted from (*26*) with permission of Elsevier.

Biodistribution studies

Ex vivo biodistribution studies are operationally more complex than *in vivo* imaging, as they involve sacrificing animals at a predetermined timepoint after dosing the radiotracer, dissecting them, and counting the individual organs in a gamma counter. This provides comprehensive biodistribution data (% injected dose per gram of tissue) that can be input into software programs, like OLINDA (*27*), to generate human dosimetry estimates that need to be included in any IND filings supporting translation of PET radiotracers into clinical studies.

Clinical Studies

Clinical studies, employing PET, most frequently make use of established radiotracers that are either FDA approved or investigational in use. Investigational radiotracers can be used under the approval of an institutional RDRC Committee or an FDA-approved IND depending upon the intended application (*4,28*). Approved radiotracers are used under the auspices of either a New Drug Application (NDA) or, in the case of generic drugs, an Abbreviated New Drug Application (ANDA). The different Phases of clinical trials are summarized in Table 1, and described in detail in a previous article in this series (*4*).

Table 1: Overview of the Clinical Trial Process.

Phase	# Subjects	SCOPE
0/I	Few dozen (therapeutic); 10-30 (diagnostic)	A new drug is first given to a small number of people. Studies might be exploratory, involving several candidate molecules to select a lead for development (*28*), and are intended to demonstrate safety of the new agent and the dose limiting toxicity.
II	Few hundred (therapeutic); 20-40 (diagnostic)	Undertaken to demonstrate proof of efficacy and also reveal less common side effects. If enough patients benefit from the new drug, and side effects are acceptable, then Phase III trials can be initiated. Additional safety data is obtained.
III	Several hundred (therapeutic); 50–100 (diagnostic)	Trials are intended to compare safety and efficacy of a new diagnostic or therapeutic agent against standard of care. They are typically large multicenter studies, and research subjects are picked at random to receive standard of care or the new treatment. When neither doctor or subject know which treatment the subject is getting, the trial is considered double-blinded. Additional safety data is obtained. If a new drug is found to be as or more effective as existing drugs and/or safer, then an NDA can be submitted to FDA.
IV	Thousands	Post-approval studies intended to monitor drugs approved by the FDA over a long period of time (e.g., several years).

HOW RADIOPHARMACEUTICALS CAN BE DEPLOYED IN RESEARCH

Several type of radiopharmaceuticals are utilized in imaging collaborations with pharmaceutical companies (Table 2). They include use of FDA approved products as tracers or biomarkers to study aspects of disease, investigational agents used to interrogate biological systems and functions, investigational imaging or therapeutic radiopharmaceuticals being developed for FDA approval, and radiolabeled drug compounds to study biodistribution and receptor occupancy.

The selection of an appropriate imaging agent depends upon the study in question as well as local availability. For example, different imaging agents might be used at various sites on the same clinical trial, depending upon availability from nearby commercial nuclear pharmacies.

Table 2: Types of radiopharmaceuticals used in clinical trials and examples.

Types of Radiopharmaceuticals Used in Clinical Trials	**Examples**
FDA approved imaging radiopharmaceuticals for diagnosis, staging, monitoring of therapy, or as biomarker/surrogate endpoint	^{18}F-FDG ^{18}F-florbetapir [Amyvid® - Eli Lilly] ^{18}F-florbetaben [Neuraceq® - Life Molecular Imaging] ^{18}F-flutemetamol [Vizamyl® - GE Healthcare] ^{18}F-flortaucipir [Tauvid™ - Eli Lilly] ^{68}Ga-DOTATATE [NETSPOT® - Advanced Accelerator Applications] ^{64}Cu-DOTATATE [Detectnet™ Curium US LLC] ^{68}Ga-PSMA-11 [UCSF and UCLA] ^{18}F-DCFPyL [Pylarify® - Progenics Pharmaceuticals, Inc] ^{123}I-ioflupane [DaTscan™ - GE Healthcare] ^{18}F-fluciclovine [Axumin™ - Blue Earth Diagnostics] ^{8}F-fluroestradiol [CERRIANNA™ - Zionexa US Corp] ^{99m}Tc-sestamibi ^{18}F-fluorodopa [Feinstein Institutes for Medical Research] ^{68}Ga-PSMA-gozetotide [Locametz® Novartis]
FDA approved therapeutic radiopharmaceuticals	^{177}Lu-DOTATATE [Lutathera® - Advanced Accelerator Applications] ^{177}Lu-PSMA-617 [PLUVICTO® Novartis]
Investigational agents for research use under RDRC or IND	^{11}C- Pittsburgh Compound B (PIB) ^{18}F-fluorothymidine (FLT)

	^{18}F-(–)5-fluoroethoxybenzovesamicol (FEOBV)
Investigational imaging and therapeutic agents being developed for commercialization	^{18}F-flupiridaz (FPZ) (imaging) ^{225}Ac-PSMA-617 (therapy)
Investigational radiotracers developed to support therapeutic trials (e.g., receptor occupancy)	^{18}F-SPA-RQ
Radiolabeled drugs or drug candidates	^{11}C-ibrutinib ^{11}C-docetaxel ^{18}F-lansoprazole

FDA approved imaging radiopharmaceuticals for diagnosis, staging, monitoring of therapy,

Approved radiopharmaceuticals can be used for diagnosis of disease, staging, and monitoring of response to therapy (experimental or approved). Importantly, if patients respond to therapy they continue receiving the same treatment, while if they do not respond they can be switched to alternate therapies rapidly, saving both time and money, and reducing duration of unnecessary side effects. Pioneering work was conducted by Dr. Annick Van den Abbeele, MD, and colleagues at the Dana-Farber Cancer Institute to diagnose and treat gastrointestinal stromal tumors (GIST) (*29*). FDG-PET can be used to diagnose, localize and stage GISTs, and also monitor response to Gleevec (imatinib) therapy (Figure 3). The functional information on tumor metabolism of glucose from serial FDG scans can be employed to detect both short-term and long-term tumor responses that may not be obvious with CT. The team noted that FDG-PET responses were apparent even 24 h after the first dose of imatinib. Significant changes in FDG uptake (>25% decrease in SUV_{max} relative to baseline) were apparent within 1 month of starting imatinib therapy in all GIST patients who responded. In the event patients did not respond, then this was quickly apparent in the PET scans, such that treatment could be changed to sunitinib (Sutent), which is a second drug approved for treatment of GIST to which this patient subtype may be more sensitive.

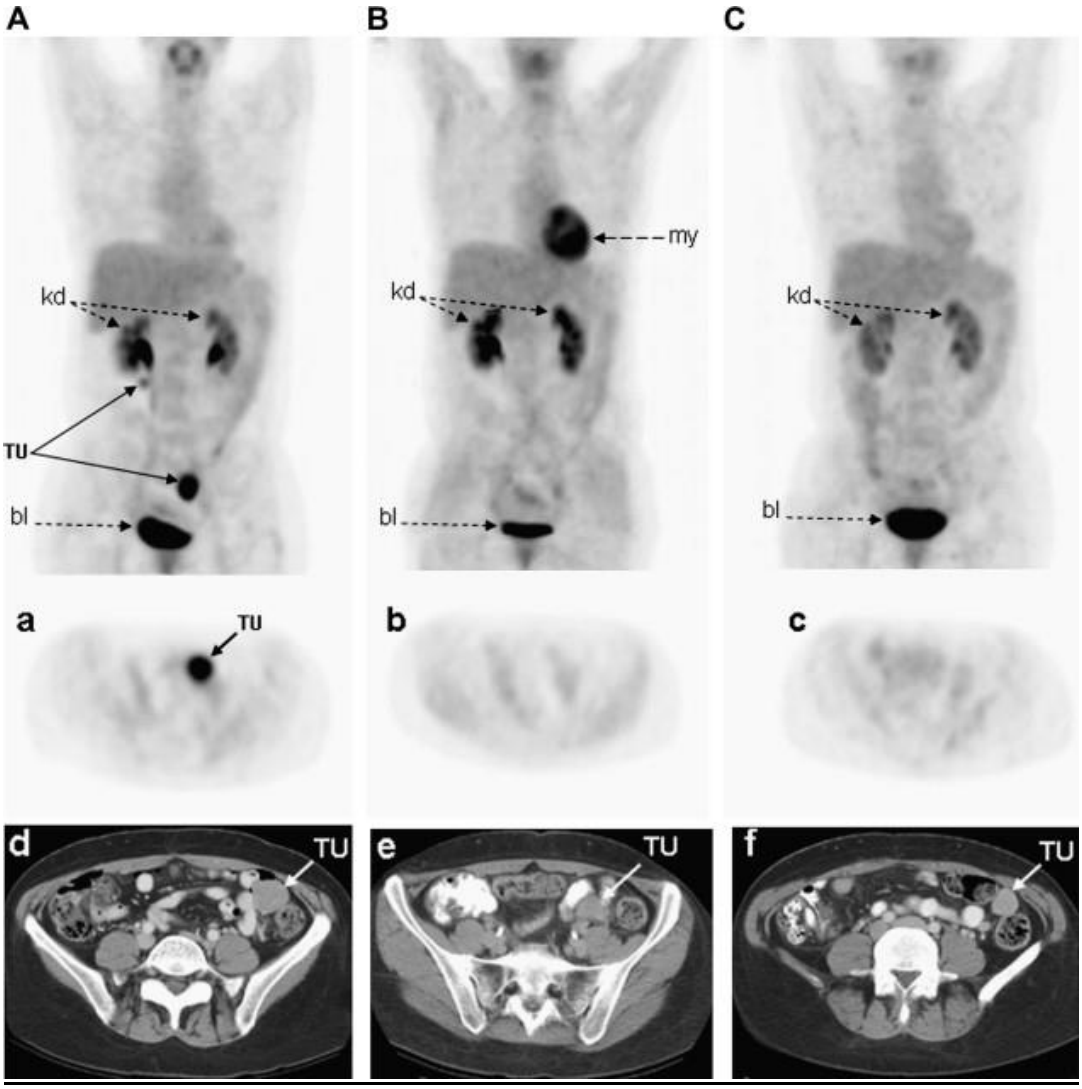

Figure 3: FDG-PET maximum intensity projection images (A–C), axial PET (a–c), and axial CT (d–f) slices through the pelvis in a patient with metastatic GIST. Normal physiologic FDG uptake is seen (*dashed arrows*) in the urinary collecting system in both kidneys (kd), the myocardium (my), and in the bladder (bl). (*A*) Intense FDG uptake is seen in the left lower pelvis and contiguous to the right proximal ureter (TU, *straight arrows*) at baseline before imatinib therapy consistent with metastatic GIST. (*B*) Resolution of abnormal FDG uptake is noted in both tumor masses as early as 1 week following treatment. (*C*) Continuous metabolic response to imatinib is seen in this patient 2 months following initiation of therapy despite the presence of a residual mass on CT. Reprinted from (*29*) with permission of Elsevier.

Use of FDA approved imaging agents as biomarkers/surrogate endpoints in clinical trials

A recent example of using PET radiotracers to support therapeutic trials utilized the use of amyloid imaging (Amyvid®, Vizamyl®, Neuraceq®) and tau (Tauvid™, MK6240) PET to support development of Alzheimer's disease (AD) therapeutics like aducanumab. Such therapeutic agents are recombinant human monoclonal antibodies that bind aggregated forms of amyloid beta that form the hallmark amyloid plaques found in AD. PET imaging played a crucial role in confirming initial eligibility for participation of a given patient in a clinical trial, and also monitoring subsequent response to therapy. In clinical trials of aducanumab, amyloid PET revealed decreases in beta amyloid neuritic plaque accumulation upon treatment (*30*) (Figure 4).

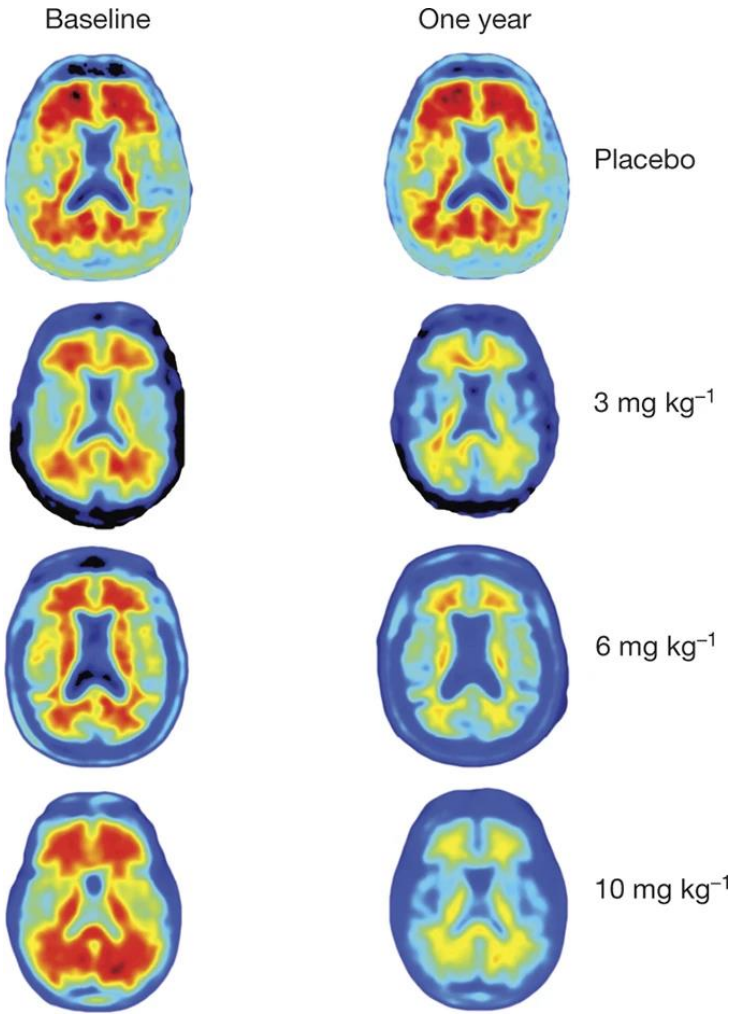

Figure 4: [^{18}F]Florbetapir [Amyvid®] amyloid PET images at baseline and one year following aducanumab treatment, showing amyloid plaque reduction following different doses of aducanumab, but not placebo. Reproduced from (*30*) with permission from Nature Publishing Group.

Investigational agents for research use under RDRC or IND

Imaging agents can be used for research applications under the approval of an institutional RDRC (*31*) or an approved IND (*32*). To utilize a radiotracer according to the RDRC mechanism, the following provisions must be met:

- The research is considered basic science research and is done for the purpose of advancing scientific knowledge;
- The research study is authorized by an FDA-approved RDRC;
- The pharmacologic dose of the radioactive drug is known not to cause any clinically detectable pharmacologic effect in humans;
- The radiation dose to be administered is justified by the quality of the study and the information it seeks to obtain.

If these provisions cannot be met, then an approved IND application is required for the agent prior to conducting any human research (*33*, *34*). Academic medical centers frequently have many established radiotracers available for use in RDRC protocols, and likely also hold IND approvals for several additional radiotracers. Additional research protocols can be added to INDs by submission of amendments to FDA. After a radiotracer has been used in humans under an IND, it can either be advanced to additional clinical trials with a goal of commercialization (see below). Alternatively, if the pharmacologic dose did not cause any clinically detectable pharmacologic effects, it can subsequently be transitioned to RDRC studies for additional research, assuming the other criteria are met as outlined above.

The transition from RDRC to IND can be illustrated with ^{18}F-(–)5-fluoroethoxybenzovesamicol (^{18}F-FEOBV), a PET radiotracer based upon a vesamicol analogue used to image the vesicular acetylcholine transporter that was developed at the University of Michigan (*35*). Following preclinical development along the lines described above, the team wrote an IND and received approval from FDA to proceed with first-in-human studies. Whole-body ^{18}F-FEOBV scans were initially conducted in 3 healthy human volunteers. Seven additional subjects underwent dynamic brain imaging (Figure 5, left), and kinetic modeling revealed agreement between reference tissue modeling and late single-scan imaging. This study allowed quantification of human dosimetry, indicating that > 400 MBq could be administered without exceeding radiation dose limits. No pharmacologic or physiologic changes were observed after intravenous administration of ≤1.3 μg of FEOBV. These latter two data points subsequently

enabled use of ^{18}F-FEOBV under RDRC (and related mechanisms in other countries) by other research teams in the US and elsewhere (*36*, *37*, *38*). For example, Kanel and colleagues recently used FEOBV to investigate age-related declines of regional cholinergic neuron terminal density (Figure 5, right*)(39)*.

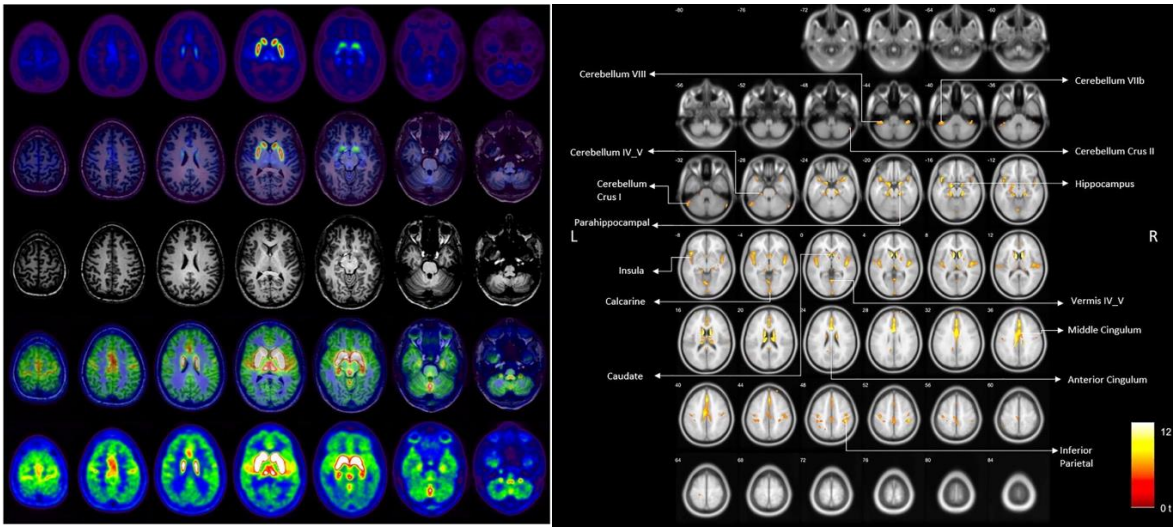

Figure 5: FEOBV PET, MR, and overlay images from healthy control subject (left, reprinted from (*35*) © SNMMI); Age-related reduced VAChT binding reductions are shown (right, reprinted from (*39*) under the terms of the Creative Commons Attribution License (CC BY-NC-ND 4.0)).

Investigational imaging and therapeutic agents being developed for commercialization

Development of new radiopharmaceuticals for commercialization follows the process illustrated in Figure 1. Since companies do not have access to research subjects, clinical trials are usually conducted in collaboration with academic medical centers. Following preclinical work, an IND is obtained to enable clinical trials with new agents to prove safety and efficacy. High profile examples are the theranostic agents targeting prostate specific membrane antigen (PSMA) for imaging and treatment of prostate cancer. In the case of ^{68}Ga-PSMA-11, following pioneering work from Heidelberg, University of California Los Angeles and University of California San Francisco obtained an NDA for ^{68}Ga-PSMA-11 through an academic partnership (*40*). They conducted a Phase III trial and separate NDAs for each institution were approved by FDA. Subsequent approvals for kits to produce ^{68}Ga-PSMA-11 have been obtained by Telix and Novartis, and the agent has been used to image thousands of patients (*41*).

Concurrent with these efforts ^{177}Lu-PSMA-617 was developed for radiotherapy of prostate cancer. PSMA PET is used to confirm patient eligibility and monitor response to therapy. Phase 2 studies showed promising results (Figure 6) (*42*), and the rights for development were acquired by Endocyte (later purchased by Novartis). In the large international multicenter Phase 3 VISION trial, 831 patients underwent randomization. VISION provided evidence for significantly improved progression-free and overall survival in late-stage prostate cancer patients who were treated with ^{177}Lu-PSMA-617 (compared to standard of care) (*43*, *44*). FDA approval for ^{177}Lu-PSMA-617 was granted earlier this year.

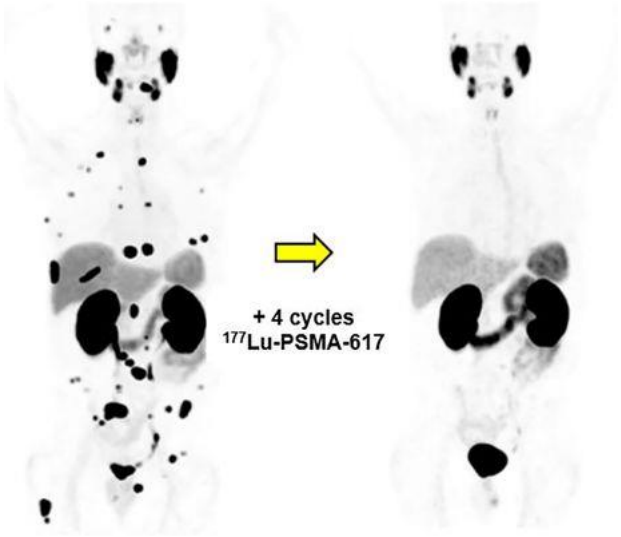

Figure 6: ^{68}Ga-PSMA-11 PET before and after treatment with ^{177}Lu-PSMA-617, reprinted from (*42*) © SNMMI

New radiotracers developed to support therapeutic trials

If radiotracers do not exist for a given therapeutic target, it is necessary to develop the appropriate companion diagnostic when PET studies are needed. One of the seminal reports of using PET imaging to guide therapeutic development is Merck's work with Emend® (aprepitant), a neurokinin 1 receptor antagonist being developed for both treatment of chemotherapy–induced nausea, and as an antidepressant. Instead of labeling the drug itself, Merck developed a companion tracer, [^{18}F]SPARQ, and used it to determine receptor occupancy achieved by different doses of Emend® in healthy humans. Importantly, they found greater than 95% receptor occupancy (RO) at the proposed dose (Figure 7), indicating the correct dose selection. Merck knew this dose was effective for managing nausea caused by chemotherapy, moved forward with the anti-nausea indication, and gained marketing approval from FDA. In contrast, Merck also knew the study dose of Emend® had no anti-depressant effects and the PET study revealed a larger dose would not increase RO. As such, the results of this study (likely costing tens of thousands of dollars) allowed them to cancel development of Emend® for depression and save millions of dollars on what would have been a futile Phase III trial (*45*).

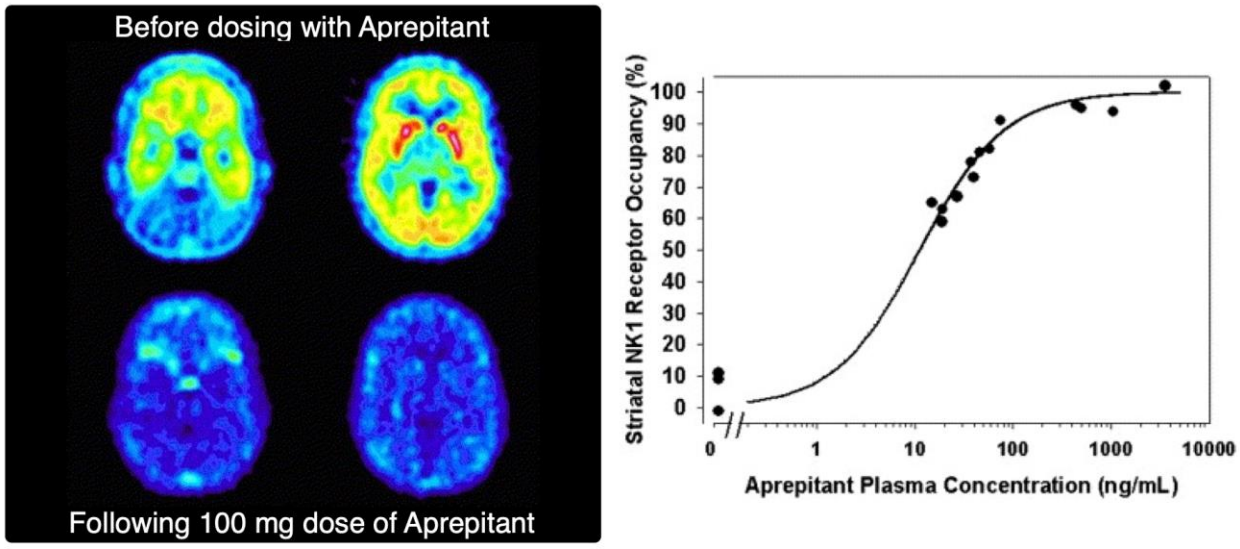

Figure 7: Left – [^{18}F]SPARQ PET image from a subject who received 100 mg aprepitant: Pre-dosing (top row) and post-dosing (bottom row), estimated receptor occupancy = 94%. **Right** - relationship between plasma concentration of aprepitant and receptor occupancy. Reprinted from (*45*) with permission of Elsevier.

Radiolabeled drugs or drug candidates

Important questions concerning a drug can be answered by labeling the drug molecule itself. Clinical imaging studies using labeled drugs allow drug developers to obtain information about biodistribution and target engagement. This information can be used to confirm patient eligibility for a given treatment, as well as to predict response. This approach holds particular promise for anti-cancer drugs. In a given malignancy, certain chemotherapeutics will be used based upon demonstrated clinical efficacy (e.g. tumor response, improved survival etc.). Historically, this has been done in a “one-size-fits-all” approach, where patients will be started on a standard regimen for their cancer. However, failure of a given chemotherapeutic occurs in certain patients because many cancers do not respond consistently. This means non-responders are often subjected to the psychological burden of chemotherapy along with frequent associated toxicities without gaining any benefit. A new era of chemotherapy is needed in the age of personalized medicine which abandons this “one-size-fits-all” approach, and molecular imaging has an important role to play in this paradigm shift.

Proof of concept has been demonstrated by van der Veldt and colleagues at VU University Medical Center in Amsterdam for docetaxel. This cytotoxic drug is a taxane that was initially approved for treatment of anthracycline-refractory metastatic breast cancer and has subsequently been approved for treatment of several other cancers (e.g., metastatic prostate cancer, head and neck cancer, non-small cell lung cancer). However, as noted above, cancers often do not respond consistently to chemotherapeutics. Docetaxel failure, in some patients, means that they suffer associated toxicities without any benefit. To explore a more personalized approach to decide which patients would benefit from docetaxel therapy the team prepared [^{11}C]docetaxel (*46*). Using PET imaging in conjunction with microdoses of [^{11}C]docetaxel (to eliminate toxicity concerns), the team was able to quantify tumor uptake of the labeled drug across patients. This work showed that [^{11}C]docetaxel PET can be used to predict tumor uptake of the drug during subsequent docetaxel therapy, and the team also demonstrated that high tumor uptake of [^{11}C]docetaxel was related to improved tumor response following treatment.

Going forward, PET with radiolabeled drugs will enable straightforward confirmation of target engagement in humans and, in turn, predict treatment outcome in advance. The work with [^{11}C]docetaxel also suggests radiolabeled drugs can help to reveal underlying mechanisms of treatment failure in subpopulations of patients (e.g. poor accumulation in a tumor, poor target engagement).

CONCLUSIONS

The power of nuclear medicine and molecular imaging to provide key information about new therapeutic candidates has become an integral part of the modern drug development paradigm. Preclinical studies can allow early go/no-go decisions about whether to advance a new drug to clinic trials. Following clinical translation, imaging can be employed to enrich clinical trials, predict response to therapy, monitor response, and obtain valuable information about target engagement and dosing. In this way, it is expected that nuclear

medicine and molecular imaging using radiotracers and/or radiolabeled drugs will continue to provide insights during drug development. When combined with other emerging technologies, this approach will usher in a new era of personalized medicine in which rational treatment choices tailored to improve outcomes for individual patients will replace a one-size-fits-all approach to disease management.

DISCLOSURE

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