Review

PET in neurotherapeutic discovery and development

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A B S T R A C T

Positron emission tomography (PET) is a highly sensitive, quantitative imaging technique that can track sub-nanomolar quantities of positron-emitting radionuclides throughout the body. By incorporating such radionuclides into molecules of interest, we can directly assess their pharmacokinetic and pharmacodynamic (PK/PD) characteristics *in vivo* without changing their physicochemical characteristics or eliciting a pharmacological response. As such, PET imaging has long been used as a tool to aid drug discovery programs from preclinical biomarker validation all the way through to clinical trials. In this perspective we discuss the use of PET radioligands in central nervous system (CNS) drug discovery and development, with a focus on recent applications in psychiatry (e.g. 5-HT$_2$A, 11β-HSD1), neuro-oncology (e.g. KRAS^{G12C}, ATM, ALK2), and neurodegeneration (e.g. amyloid beta plaques, MAPK p38), while exploring the intricacies associated with developing novel radiotracers for CNS targets. Examples highlight the preclinical and clinical uses of PET for studying biomarker function, drug candidate PK/PD, target occupancy/engagement, dosing regimen determination, clinical trial patient selection, and quantifying biomarker changes in response to treatments.

Introduction

Central nervous system (CNS) disorders constitute a major global health challenge. It is estimated that over 40 % of the population experienced CNS health loss in 2021, including neurodevelopmental disorders, neuro-oncology, age-related neurodegeneration, and psychiatric conditions [1]. Mental health conditions alone had an estimated 970 million cases in 2019, a near 50 % increase compared to 1990 [2]. Despite this growing epidemiological crisis, novel CNS drug development has slowed over the past few decades [3–5] because many large pharmaceutical companies divested from their CNS drug discovery pipelines in the 2010s [3] as a result of the fiscal challenges and high attrition rates associated with neurotherapeutic development.

Preclinical development for CNS drugs is notoriously difficult because the novel molecular entities must not only demonstrate efficacy and minimal off-target effects, but they must also contend with surpassing the blood-brain barrier (BBB) in sufficient levels to be therapeutically relevant [6–11]. Even once a company has a lead candidate after screening up to millions of compounds in the preclinical hit-to-lead process [6], 80–90 % of Phase I candidates do not make it through regulatory approval [12–14]. CNS drug development suffers from one of the highest rates of late-stage failure, with nearly half of all CNS drugs in Phase III being discontinued due to lack of efficacy [12–14]. Estimates place the timeline and budget for advancing a drug candidate to Phase III clinical trials in the range of 10–20 years and millions-to-billions of US dollars [6, 15]. Given the cost and high attrition rates, tools that are able to aid and de-risk the neurotherapeutic R&D process are in high demand.

Positron emission tomography (PET) is a medical imaging technique that can be used to de-risk CNS drug discovery and development [16,17]. Molecules containing positron-emitting radionuclides, known as radiotracers, are designed to target a biochemical process or specific protein (e.g. receptor, enzyme, protein aggregate, etc.). As the radiotracer travels through the body, the integrated radionuclides undergo radioactive decay, releasing a positron (β$^+$) which annihilates on contact with an electron to create two 511 keV photons traveling approximately 180° apart. These coincident photons are then detected by the scanner for reconstruction into a three-dimensional image. By creating PET-isotopologs of lead drug candidates, their pharmacokinetics and pharmacodynamics can be evaluated in vivo while maintaining their physicochemical characteristics; this includes key CNS drug factors like

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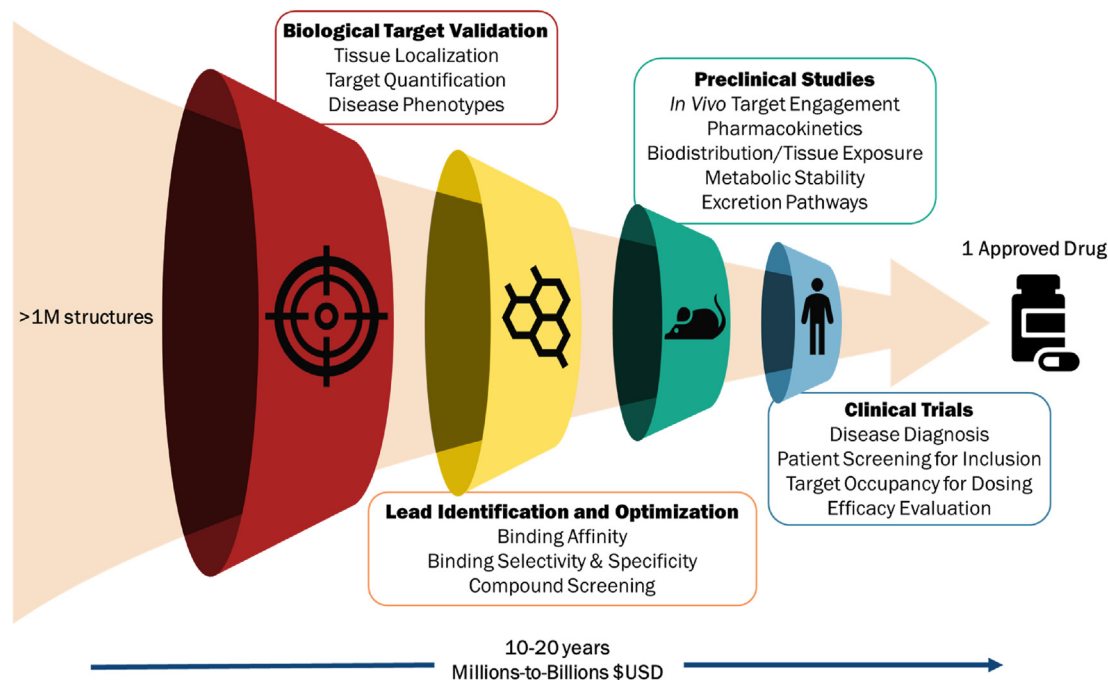
Fig. 1. Graphic depicting the drug discovery process, in which millions of chemical structures are eventually narrowed down to one approved drug – a costly and time-consuming process. 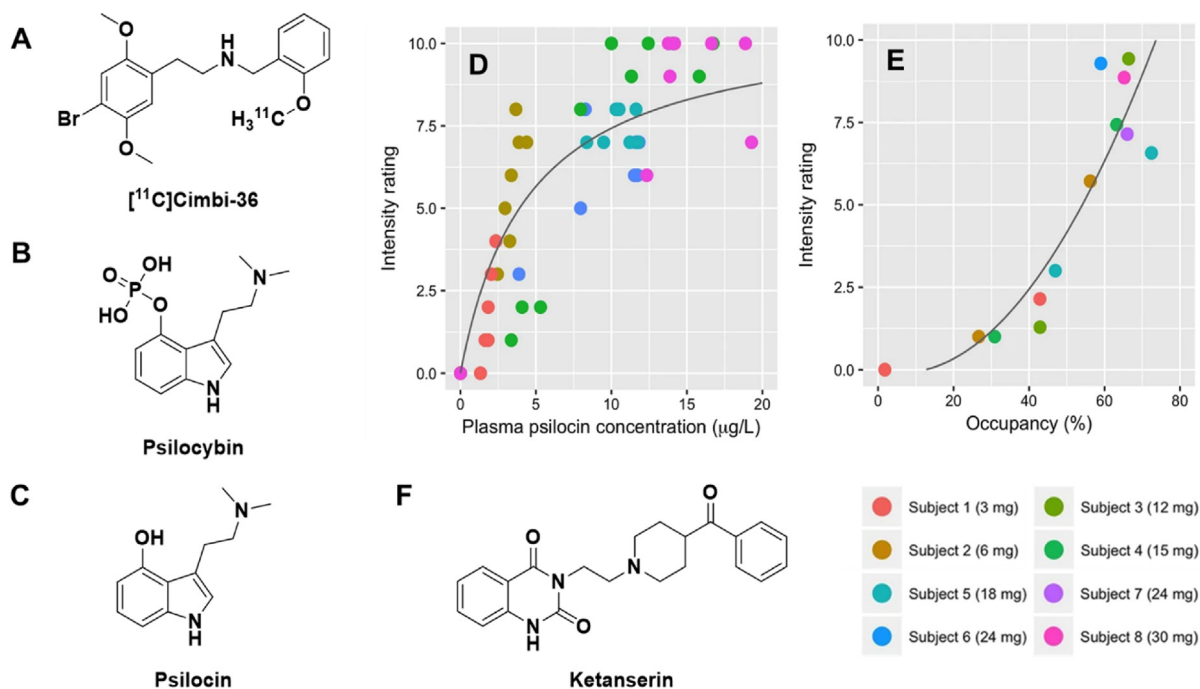The numerous ways in which molecular imaging can be applied to aid attrition rates and inform drug development at various stages are shown.

Fig. 2. (A) Structure of [^{11}C]Cimbi-36. (B) Relationship between subjective intensity rating after psylocibin dosing and neocortical 5-HT$_2$AR occupancy. (C) Relationship between subjective intensity rating and plasma psilocin concentration. Adapted from Madsen MK et al. Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. Neuropsychopharmacol 2019; 44:1328–1334. Springer Nature.

brain uptake/washout rates, drug-target engagement, target occupancy, drug metabolism, and excretion routes. Moreover, PET radiotracers are administered at sub-pharmacological doses, and are ideal for translation to non-human primates (NHPs) or human use without eliciting a pharmacological response or risking adverse effects.

In this perspective article, we offer an overview of how PET radiotracers can be applied to neurotherapeutic programs of all stages, with an emphasis on recent literature examples in the fields of neuropsychiatry,

neurodegeneration, and neuro-oncology. This current perspective article is intended to provide a short, updated view on the multifaceted uses of CNS PET in selected examples of neurotherapeutic development (Fig. 1).

Serotonin 5-HT$_2$A receptor (5-HT$_2$AR)

The popularity of psychedelic therapy has skyrocketed in recent years, with ongoing investigations into its potential for treating
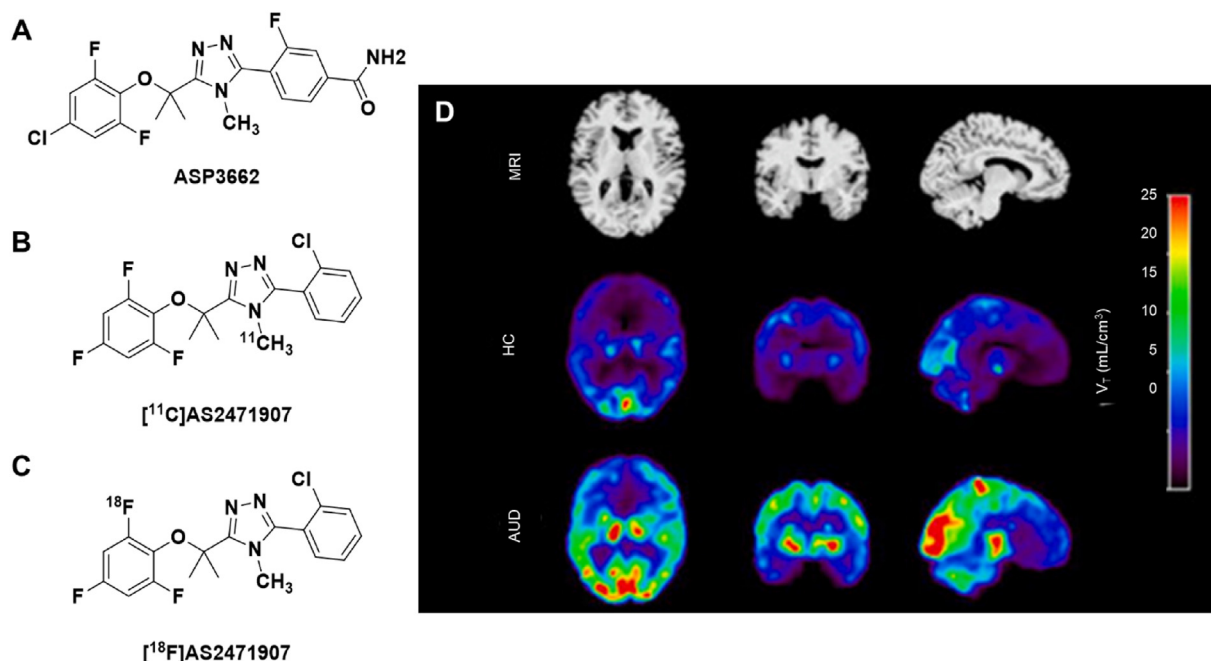
Fig. 3. Structures of 11β-HSD1 radiotracers (A) [^{11}C]AS2471907 and (B) [^{18}F]AS2471907. (C) Participant's MRI and co-registered parametric [^{18}F]AS2471907 V_T images in age-matched and sex-matched individuals with alcohol-use disorder (AUD) versus healthy control (HC). Adapted from Verplaetse TL et al. Imaging a putative marker of brain cortisol regulation in alcohol use disorder. Neurobiol Stress 2024; 29:100609. Copyright (2024), with permission from Elsevier.

conditions including anxiety disorders, post-traumatic stress disorder, substance use disorders and treatment resistant depression [18–20]. Psychedelic effects are thought to arise from stimulation of serotonin 5-HT$_2$A receptors (5-HT$_2$AR) [21], making this target of particular interest for studying the origins of phenomena such as sensory hallucination, and assessing whether these affects can (or should) be detangled from the potential benefits to mood and cognitive processes. Neuroimaging has been used extensively in this psychedelic renaissance for quantifying neurochemical changes associated with psychedelic therapy [22,23]. In particular, we highlight the role that [^{11}C]Cimbi-36 (Fig. 2A) has played in studying target occupancy and the role of 5-HT$_2$AR in psychedelic research.

[^{11}C]Cimbi-36 is a 5-HT$_2$AR agonist radioligand with quantifiable off-target affinity for serotonin 5-HT$_2$C receptors [24–26]. [^{11}C]Cimbi-36 has been used to investigate 5-HT$_2$AR target occupancy for several molecules with known serotonergic activity. Notably, this radiotracer was used to assess the relationship between the subjective psychedelic effects of psilocybin, plasma levels of its active metabolite psilocin, and 5-HT$_2$AR occupancy in healthy human volunteers [27] (Fig. 2B–E). This study found a dose-dependent association of psylocibin ingested (3–30 mg) and plasma psilocin with cerebral 5-HT$_2$AR occupancy, reporting an EC$_{50}$ for psilocin of 1.95 μg/L (or 10 nM). Moreover, neocortical target occupancy was shown to positively correlate with subjective psychedelic effect intensity ratings. Interestingly, these results support a range of 0.5–2 mg psylocibin for micro-dosing in psychedelic therapy, as that range should correspond with low target occupancies and, thus, low subjective psychedelic effect scores. These target occupancy PET studies have contributed to our current understanding of psylocibin's mechanism of action, while also providing important information for clinical trials in psychedelic therapy.

A key concern about using psychedelic treatment for psychiatric conditions is the potential for unpleasant psychedelic effects which may cause the patient significant distress and/or exacerbate the underlying psychiatric condition. To this end, a rescue drug to stop or shorten psychedelic effects could be a useful treatment tool. Ketanserin is a 5-HT$_2$AR specific antagonist known to prevent and/or terminate the subjective effects induced by certain psychedelics when used as a pre-treatment or

rescue drug (Fig. 2F) [28–31]. The selectivity of ketanserin for 5-HT$_2$ARs may provide an advantage over the current antipsychotic methods of shortening distressing psychedelic experiences that are attributed to off-target affinity for dopamine D$_2$ receptors [30,31]. The 5-HT$_2$AR target occupancy of ketanserin was measured using [^{11}C]Cimbi-36, which yielded information pertinent to its potential use as a psychedelic rescue drug [32]. The study found that orally administered ketanserin (10–40 mg) had a dose-dependent cerebral 5-HT$_2$AR occupancy with an EC$_{50}$ of 2.52 μg/L (or 6.4 nM). These findings suggest that selective 5-HT$_2$AR antagonists or inverse agonists may be preferable alternatives to the current antipsychotics being used as rescue medications for bad psychedelic experiences, while also providing neurochemical rationale that strongly supports previous rescue drug dosing regimen and drug rescue kinetics studies.

While the ongoing research in psychedelic therapy is certainly exciting, legal restrictions on controlled substances continue to hamper these studies globally. As such, readers should note that regulatory approvals and security compliance may be required to conduct psychedelic therapies and/or radiopharmaceutical production in certain jurisdictions.

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1)

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an intracellular enzyme responsible for reducing cortisone to glucocorticoid cortisol, and is widely expressed in adult prefrontal cortex, hippocampus, and cerebellar tissues [33,34]. Brain cortisol levels regulate the hypothalamic-pituitary-adrenal (HPA) axis, a major part of the neuroendocrine system that controls stress responses. Irregular cortisone metabolism has been associated with numerous psychiatric conditions, including depression, post-traumatic stress disorder (PTSD), and substance use disorders, as well as age-related cognitive decline [33–38]. Several recent clinical trials have investigated 11β-HSD1 inhibitors in CNS conditions (NCT02727699; NCT01146886; NCT01146886; NCT05657691; NCT02017444).

One clinical trial that made use of PET imaging was sponsored by Astellas Pharma, investigating the pharmacokinetics, pharmacodynamics,
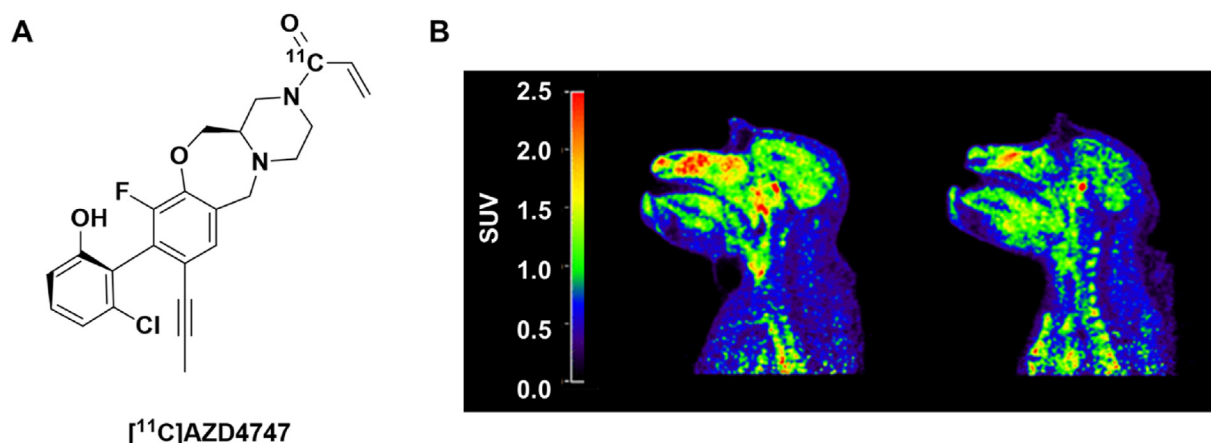
Fig. 4. (A) Structure of radiolabeled [^{11}C]AZD4747. (B) [^{11}C]AZD4747 PET images (average SUV 5–123 min) in two cynomolgus monkeys. Adapted with permission from Kettle, J.G. et al. Discovery of AZD4747, a Potent and Selective Inhibitor of Mutant GTPase KRASG12C with Demonstrable CNS Penetration. J Med Chem 2023; 66(13):9147–9160. Copyright 2023 American Chemical Society.

and safety profile of their 11β-HSD1 inhibitor, ASP3662, at single and multidose regimens in healthy volunteers (NCT02194491) (Fig. 3A). Originally, preclinical pharmacology data was used to estimate starting doses for humans; however, this led to a large range of 0.15 mg up to 10 mg [39]. Instead of adhering to this estimate, researchers turned to PET imaging to aid their clinical trial study design. Previous enzyme occupancy studies in NHPs with the 11β-HSD1 PET imaging agent [^{11}C]AS2471907 (Fig. 3B) predicted that 1 mg would inhibit between 30 % and 50 % of 11β-HSD1 activity in the brain [40,41], leading researchers to use this as their starting dose for the Phase I clinical trial. Human PET data was also collected to determine drug-target engagement within the brain and evaluate maximal enzyme inhibition levels and kinetics, although this imaging data was never published. These studies exemplify how PET can help in early phases of clinical trial design and be used to confirm drug-target interactions in the human brain.

Interestingly, the fluorine-18 labeled isotopolog, [^{18}F]AS2471907 (Fig. 3C), is being applied to studying the HPA axis in various aspects of psychiatric research, including recent articles that have shown significantly heightened 11β-HSD1 expression in prefrontal limbic brain regions in PTSD and substance use disorders compared to healthy controls (Fig. 3D) [36,37,42,43]. In this manner, PET imaging is also being used as a putative marker of brain cortisol regulation to elucidate the involvement of 11β-HSD1 in psychiatric conditions that are not currently within the scope of ongoing clinical trials, but which have potential to benefit from 11β-HSD1-related neurotherapeutic intervention in the future.

Mutant GTPase KRAS^{G12C}

Brain cancers have among the lowest survival rates of any cancer [44, 45]. The blood-brain barrier is a highly selective endothelial barrier which restricts the passage of chemotherapeutics from peripheral blood flow to CNS fluids, thereby precluding the use of many peripherally active chemotherapeutics. Even if chemotherapies are able to pass the blood-brain barrier, many primary CNS tumors exhibit inherent multi-drug resistance. Common cell-cycle checkpoint deficits and activated DNA damage response pathways also contribute to treatment resistance against radiotherapy and chemotherapy [45]. These overlapping resistance mechanisms contribute to poor prognoses for primary and secondary CNS tumors, and a desperate need for improved treatment methods.

The *KRAS* gene is one of three members in the rat sarcoma viral oncogene family (Ras) and encodes for the KRas (Kirsten RAS) GTPase enzyme. Oncogenic mutations in Ras proteins are found in up to 30 % of human cancers, with KRas being the most commonly mutated isoform [46]. Recently, researchers at AstraZeneca discovered a potent inhibitor

selective for the glycine to cysteine mutation at codon 12 of the K-Ras GTPase (KRAS^{G12C}) [47]. It was hypothesized that this inhibitor could be used as a chemotherapy for secondary brain metastases if it demonstrated sufficient CNS exposure. Preliminary rodent studies demonstrated a mean brain $K_{pu,u} = 0.1$, which could be elevated to a $K_{pu,u}$ of 1.0 when co-administered with a P-glycoprotein inhibitor, thereby raising concerns over potential active drug efflux in vivo. By radiolabeling the lead drug compound with carbon-11 ([^{11}C]AZD4747, Fig. 4A), the researchers were able to perform a "micro-dosing study" in NHPs to safely assess its CNS exposure in higher species without the risk of toxic effects. The results demonstrated that the compound was able to permeate through the blood-brain barrier (Fig. 4B), sporting an estimated mean brain $K_{pu,u} = 1.6$, and suggesting that this compound might cross the intact human BBB in high enough quantities to be pharmacologically active. This case highlights how PET imaging can be used to safely assess pharmacodynamic properties of candidate neurotherapeutics in higher species.

Ataxia-telangiectasia mutated kinase (ATM)

A similar study by the same group recently reported on the use of PET for developing brain penetrant ataxia-telangiectasia mutated (ATM) kinase inhibitors [48]. *In vitro* assays have shown that ATM inhibition leads to chemo- and radio-sensitizing effects in human glioma cells, making this target of interest for treating primary brain tumors [49]. In this study, the AstraZeneca ATM inhibitor clinical candidate (AZD0156, Fig. 5A) was tweaked with the intention of improving brain uptake, especially to decrease its known drug efflux activity [48]. After lead optimization, two novel ATM inhibitors were radiolabeled with carbon-11 to assess their CNS exposure compared to the clinical candidate (Fig. 5B,C). Both structures demonstrated promising $K_{p,uu} > 0.3$, unlike AZD0156, which showed low brain exposure. Ultimately, AZD1390 was selected for progression based on cell potency, kinase selectivity, and preclinical pharmacokinetic profile. In this case, [^{11}C] AZD1390 was pursued even further and assessed in healthy human volunteers, which demonstrated that this novel ATM inhibitor structure is able to cross the intact human blood-brain barrier [50]. These PET studies contributed to the progression of the new clinical candidate AZD1390 into Phase 0/1b (NCT05182905) and Phase 1 (NCT03423628) clinical studies to explore the radiosensitizing effects of ATM inhibition in intracranial malignancies [51].

Activin-receptor like kinases (ALK)

Another family of proteins that are of interest in neuro-oncology are the activin-receptor like kinases (ALKs) [52]. Seven types of ALKs have
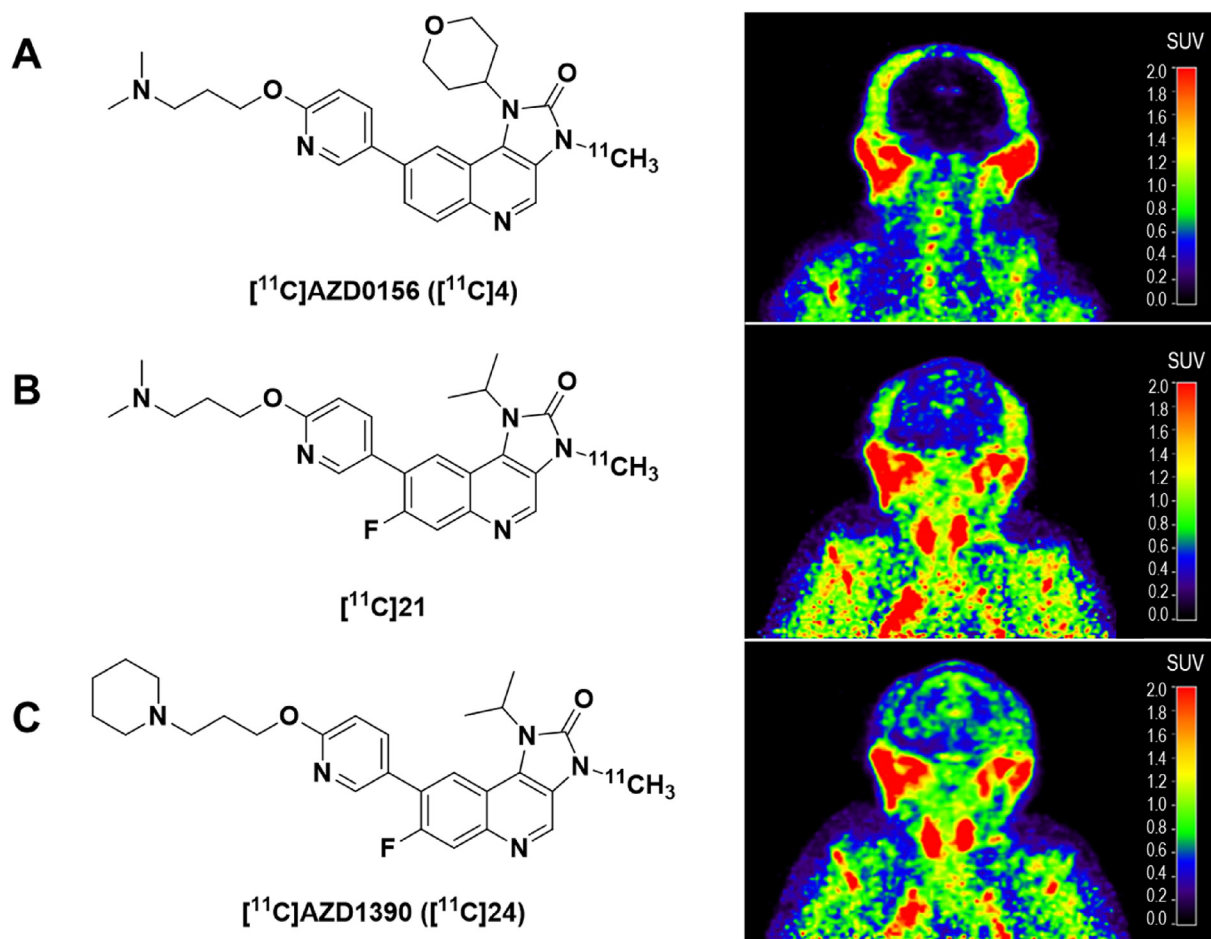
Fig. 5. Structures of (A) [¹¹C]AZD0156 ([¹¹C]4), (B) [¹¹C]21, and (C) [¹¹C]AZD1390 ([¹¹C]24) with their respective summed 5–123 min PET images in NHPs. Adapted with permission from Pike KG et al. Identification of Novel, Selective Ataxia-Telangiectasia Mutated Kinase Inhibitors with the Ability to Penetrate the Blood–Brain Barrier: The Discovery of AZD1390. J Med Chem 2024; 66(13):9147–9160. Copyright 2024 American Chemical Society.
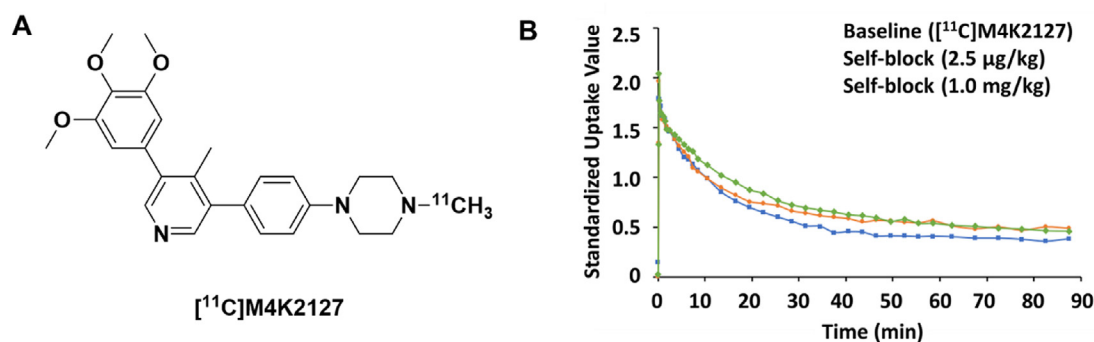
Fig. 6. (A) Structure of [¹¹C]M4K2127. (B) [¹¹C]M4K2127 PET images (average SUV 0–90 min) in a healthy rodent. Adapted with permission from Chassé M et al. Leveraging Open Science Drug Development for PET: Preliminary Neuroimaging of ¹¹C-Labeled ALK2 Inhibitors. ACS Med Chem Lett 2021; 12:846–850. Copyright 2021 American Chemical Society.

been identified in humans (ALK1-7), each with their own biological functions related to development (e.g. vasculogenesis, osteogenesis, chondrogenesis, etc.) and reproductive function. Aberrant ALK performance has been linked to several types of cancers, both as tumor promoters and suppressors. Within the realm of primary CNS cancers, deviations in certain types of ALK performance have been associated with gliomas, glioblastomas, and pituitary cancers. As such, there is much interest in developing chemotherapies for treating primary tumors or metastases within the CNS.

Mutations in the *ACVR1* gene encoding for ALK2 occur in 25–33 % of patients with the rare pediatric cancer diffuse intrinsic pontine glioma (DIPG), with many being gain-of-function over-activating mutations [52–54]. Preliminary preclinical studies suggest that ALK2 may be a promising therapeutic target [55], which has led to extensive medicinal chemistry efforts dedicated to developing novel ALK2 inhibitors [56–61]. With no adequate method of determining pons-specific exposure, our laboratories turned to carbon-11 radiolabeling of a few lead 3,5-diphenylpyridine structures for preliminary studies in rodents [62]. The
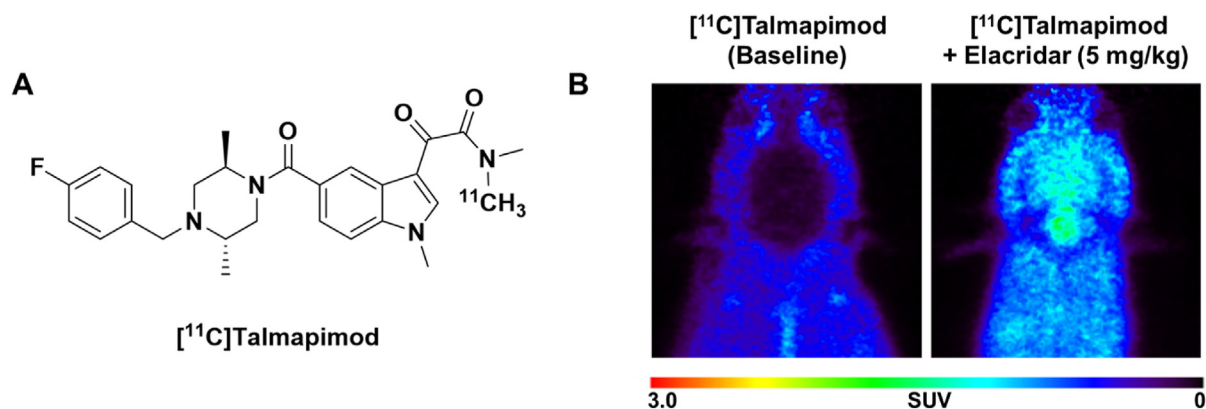
Fig. 7. (A) Structure of [11C]talmapimod. (B) [11C]Talmapimod PET images (average SUV 0–90 min) in healthy rodent at baseline and after P-glycoprotein drug efflux transporter inhibition with 5 mg/kg elacridar administered 30 min prior to radiotracer injection. Adapted with permission from Chassé M et al. In vitro and in vivo evaluation of [11C]M4K2127 for PET imaging activin receptor-like kinase 2. Nucl Med Biol 2023; 126: 108677.

most promising compound appeared to be [11C]M4K2127, with high initial brain radioactivity uptake, including homogenous uptake throughout the pons (SUV ~2) (Fig. 6A). However, subsequent preliminary homologous blocking studies *in vivo* revealed that the observed radioactivity uptake was primarily non-specific binding, with no significant change in brain uptake or washout kinetics at blocking doses of between 0.001 mg/kg to 1 mg/kg (Fig. 6B) [63]. Radiometabolite analyses showed that only ~25 % of the radioactivity in rodent brain homogenate was intact [11C]M4K2127 at 15 min post-radiotracer injection; the observed metabolic instability was further supported by poor microsomal stability [57]. This case study demonstrates the utility of PET imaging for characterizing important pharmacokinetic and pharmacodynamic properties of potential drug candidates, including metabolic stability. For PET chemists, it also highlights the importance of fully characterizing a radiotracer's in vivo characteristics, including assessment of potential confounding brain-penetrant radiometabolites [64].

Mitogen activated protein kinase p38α/β (p38α/β)

The p38α kinase has shown clinical and preclinical promise as a druggable target in several inflammatory conditions, including neurodegenerative disease [65,66]. Adverse effects reported in previous clinical trials using talmapimod for peripheral inflammatory conditions suggested that the inhibitor may be CNS permeable, with reports including dizziness, somnolence, nausea, neuropathy, and headache [67–69]. If this existing clinical trial candidate had significant CNS exposure, it could potentially be repurposed for treating neurodegenerative inflammation at lower doses.

To assess the brain uptake of intravenously administered talmapimod, the structure was recently radiolabeled in our labs with carbon-11 (Fig. 7A) and evaluated preclinically in rodents [70]. PET imaging with [11C]talmapimod revealed low baseline brain uptake (0.2 SUV); however, disrupting P-glycoprotein (P-gp) drug efflux transporter activity through pretreatment with elacridar enabled [11C]talmapimod to pass the blood–brain barrier (>1.0 SUV) [71] (Fig. 7B). A subsequent MDCK-MDR1 assay confirmed the drug efflux activity of this compound (efflux ratio of 10.2), suggesting that talmapimod is unlikely to exhibit large degrees of CNS exposure in humans. Even after surpassing the observed drug efflux activity, [11C]talmapimod exhibited poor specific binding in vivo and in vitro (<15 %), suggesting that the degree of drug-to-target interactions under neurophysiological conditions may not be ideal for therapeutic purposes. In this example, PET was a useful investigational tool to determine the potential of repurposing a known compound for CNS conditions. Through preclinical PET imaging studies, talmapimod could reasonably be discounted as a potential neurotherapeutic because of discovered drug efflux activity and poor specific binding.

Amyloid beta plaques

The neurological hallmarks of Alzheimer's disease (AD) are the presence of amyloid beta plaques, hyperphosphorylated tau aggregates, and neuronal loss – otherwise known as the 'A/T/N' criteria (amyloid/tau/neurodegeneration) – although the addition of other relevant biomarkers is an active area of research [72–75]. While multi-tracer approaches are needed for PET imaging of AD and related dementias [76–80], here we will focus on how PET has been useful for neurotherapeutic development related to amyloid plaques. The amyloid hypothesis suggests that amyloid plaque related toxicity is the primary cause of neuronal loss which results in AD progression [81,82]. Over the past several decades, many failed attempts have been made to target amyloid plaque formation and/or clearance as a means of treating AD. The lack of success of these amyloid-targeting therapies are hypothesized to arise from inappropriate in vivo characteristics, including lack of brain exposure, poor target engagement, lack of specificity, and/or improper patient selection for clinical trials [82].

Recently two monoclonal anti-amyloid antibodies, lecanemab (Leqembi®) and aducanumab (Aduhelm®), were approved in the United States through the Food and Drug Administration (FDA) accelerated approval mechanism. Amyloid PET imaging has played an instrumental role in the research and approval of these disease modifying therapies and continues to play a pivotal role in ongoing research in this area [83–88]. The radiotracers primarily used in this space are the three FDA-approved amyloid PET radiopharmaceuticals, Amyvid® (AV-45; [18F]fluorbetapir, 2012), Neuraceq® (AV-1; BAY-94-9172, [18F]florbetaben, 2014), and Vizamyl® (GE-067, [18F]flutemetamol, 2013) (Fig. 8).

In many trials, amyloid PET imaging was used as part of the inclusion criterion to ensure that patients enrolled in the clinical trial expressed the target in sufficient quantities to test the therapeutic potential of these antibodies. Moreover, PET imaging permits researchers to directly quantify biomarker expression in the brain instead of having to rely solely on peripheral measures, like protein levels in blood plasma or cerebral spinal fluid, to estimate brain amyloid plaque levels [89,90]. As a result, changes in brain amyloid can be used as a measure of treatment response, and further correlated with other measures to support claims of disease modification through slowing of clinical decline. It should be noted that, while the claims of efficacy, clinical utility of some anti-amyloid treatments, and dosing regimens remain the subjects of much debate [91–93], there is no question that these antibodies do lead to a clear reduction in brain amyloid plaque load (Fig. 8A,B). Ultimately, the accelerated approvals of both lecanemab and aducanumab relied heavily on the integral use of PET imaging in patient selection, data collection, and treatment response monitoring.
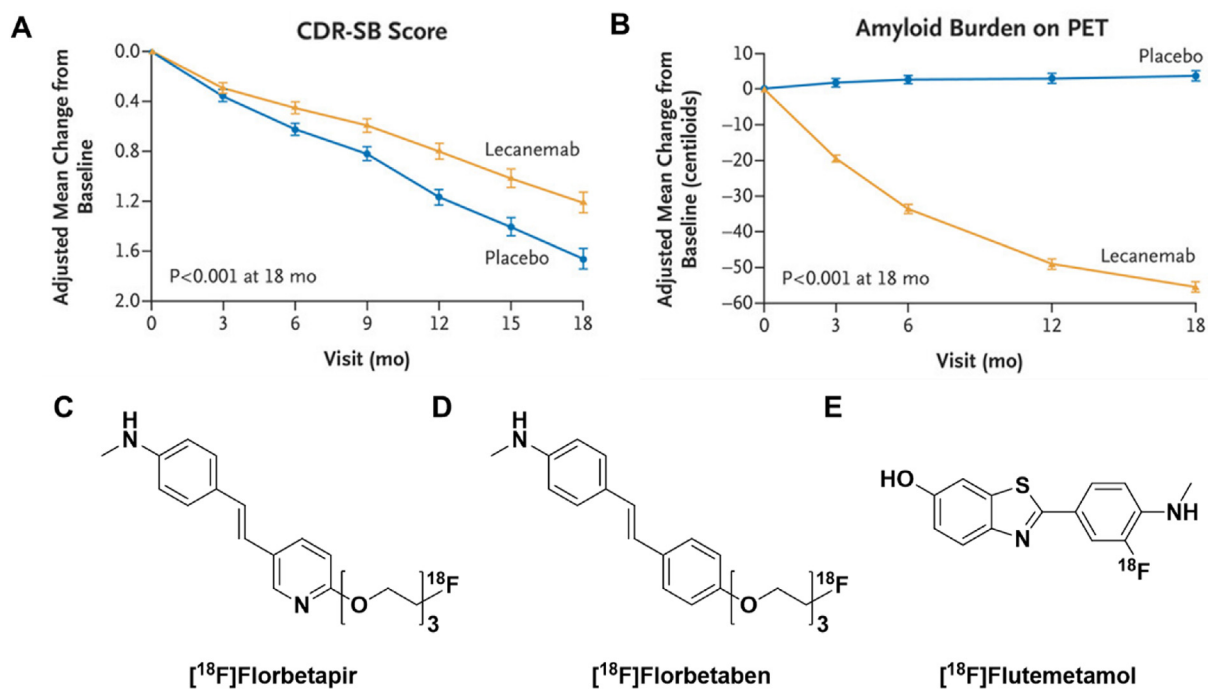
Fig. 8. (A) Change in the score on the Clinical Dementia Rating (CDR)–Sum of Boxes (CDR-SB) from baseline in an 18-month, multicenter, double-blind, phase 3 trial of lecanemab in patients with early AD versus placebo group. (B) Adjusted mean change in amyloid burden in treatment versus placebo groups as measured by amyloid PET using (C) [18F]florbetapir (Amyvid®), (D) [18F]florbetaben (Neuraceq®), or (E) [18F]flutemetamol (Vizamyl®). Graphical data adapted with permission from van Dyck et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med 2023; 388:9–21.
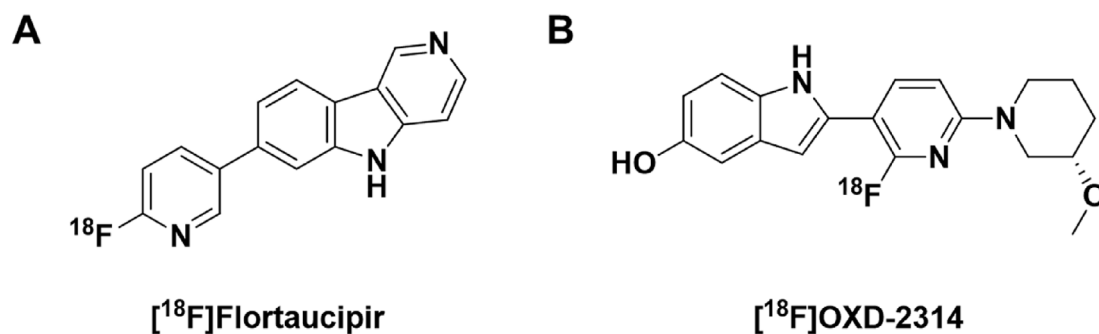
Fig. 9. (A) Structure of [18F]Flortaucipir (Tauvid™, [18F]AV-1451, [18F]T807). (B) Structure of [18F]OXD-2314.

While amyloid has paved the way for clinical applications of PET imaging for neurotherapeutic development in AD, the radiotracer Tauvid™ (a.k.a. [18F]flortaucipir, [18F]AV-1451, [18F]T807) was approved by the FDA for clinical imaging of aggregated tau in 2020 (Fig. 9A). This approval has opened the door for clinical tau burden imaging, with tau PET radiopharmaceuticals are now actively being used to de-risk neurotherapeutic development in AD programs [94]. However, it is important to recognize that tau aggregates take different forms depending on the disease. Many of the well-established tau PET tracers were developed for AD and demonstrate limited utility for imaging non-AD tauopathies (e.g. progressive supranuclear palsy, corticobasal degeneration, chronic traumatic encephalopathy, Pick's disease, etc). Novel tau PET agents developed for non-AD tauopathies are actively being developed to satisfy these gaps, including [18F]OXD-2314, which we recently translated for first-in-human studies (Fig. 9B) [95].

PET imaging has been widely used as a tool for the development and evaluation of neurotherapeutics. In this article, we showcase a few recent examples of the ways that PET imaging can aid drug discovery and development programs. For instance, recent efforts in imaging psychiatric disease have demonstrated how radiotracers can be employed for studying biomarker function, performing target occupancy and engagement studies, and determining appropriate dosing regimens (e.g. [11C]Cimbi-36, [11C] AS2471907, [18F]AS2471907). Novel radiotracers developed for neuro-oncology and neurodegeneration emphasized the utility of PET for assessing drug pharmacokinetics and pharmacodynamics, including brain permeability, drug efflux effects, and metabolism (e.g. [11C]AZD4747, [11C]M4K2127, [11C]Talmapimod). In later stages of neurotherapeutic development, PET imaging can enable effective patient population selection, and direct quantification of biomarker changes in response to treatment, as was shown with FDA-approved radiopharmaceuticals for imaging Alzheimer's disease. From biomarker validation through to clinical studies, PET imaging is a versatile tool that can be used to support and inform CNS drug development programs.

Author Contributions

M.C.: conceptualization, writing, figures, and editing. N.V.: conceptualization, supervision, and editing. Both authors reviewed the manuscript.

Declaration of competing interest

Acknowledgments

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