Research Report

α-synuclein Imaging: A Critical Need for Parkinson’s Disease Research

Jamie L. Eberling*, Kuldip D. Dave and Mark A. Frasier
The Michael J. Fox Foundation for Parkinson’s Research, New York, NY, USA

Abstract. The development of an α-synuclein imaging agent could be transformative for Parkinson’s disease research and drug development. The ability to image α-synuclein in the brain would enable tracking of the degree and location of pathology over time and monitoring of therapies aimed at reducing α-synuclein levels. The Michael J. Fox Foundation has assembled a consortium of researchers to develop an α-synuclein radiotracer for use in positron emission tomography (PET) imaging studies. While this poses a number of challenges they should not be insurmountable and lessons learned from the development of tau radiotracers should provide valuable insights.

Keywords: α-synuclein, positron emission tomography, radiopharmaceutical, biomarker, β-amyloid, tau

The ability to image α-synuclein deposition in the brain would be a game-changing achievement for the Parkinson’s disease (PD) field. The accumulation of aggregated α-synuclein is a pathological hallmark of PD and a priority target for drug development given its hypothesized contribution to neurodegeneration [1]. In vivo imaging of α-synuclein pathology could be useful as a biomarker of the presence of disease and disease progression and as a pharmacodynamic tool for drug development. Currently, α-synuclein deposition in the brain can only be studied at autopsy or inferred from levels detected in blood or cerebrospinal fluid [2]. Given these challenges and the impact such a tool would have for accelerating development of new treatments for PD, The Michael J. Fox Foundation (MJFF) has committed significant resources to the development of an α-synuclein positron emission tomography (PET) tracer.

The development of Pittsburgh Compound-B (PIB), the first highly specific β-amyloid PET tracer, transformed Alzheimer’s disease (AD) research by enabling the detection and quantification of fibrillar β-amyloid deposits in the brain and the in vivo examination of relationships between amyloid deposition, clinical symptoms, and structural and functional brain changes. While PIB has been an incredibly useful research tool, its carbon-11 (11C) label, which has a half-life of just 20.4 minutes and therefore requires an onsite cyclotron and extensive radiochemistry capabilities, restricts the use of PIB to those centers with these capabilities. Thus, there have been a number of efforts to develop comparable fluorine-18 (18F) labeled tracers which would enable widespread use of β-amyloid imaging. The 18F tracers include 18F-3′F-PIB (flutemetamol), 18F-AV-1 (florbetaben), 18F-AZD4694, and 18F-MK-3328, all of which are undergoing Phase II or Phase III clinical testing, while 18F-AV-45 (florbetapir) was approved by the FDA last year for adults being evaluated for AD or other causes of cognitive decline [3] to aid in the differential diagnosis.

β-amyloid imaging has led to insights regarding the contribution of β-amyloid pathology to the progression of cognitive decline, from normal cognitive function,
to mild cognitive impairment (MCI) and dementia. α-synuclein imaging could similarly lead to insights regarding the contribution of α-synuclein pathology to the clinical symptomatology of PD as well as to other synucleinopathies and could help distinguish Lewy body dementia from AD. While α-synuclein imaging could be a useful diagnostic marker and would likely not be subject to up and down regulation in response to PD treatments, it is true for dopaminergic imaging tracers, a positive α-synuclein scan would not be specific to PD as α-synuclein pathology is observed in several other disorders, including Lewy body dementia, multiple system atrophy, and progressive supranuclear palsy. Thus, imaging alone would not be sufficient to make a positive diagnosis of PD but would be useful when combined with a clinical examination and possibility additional imaging techniques.

β-amyloid imaging has been used as a secondary outcome measure in immunotherapy trials aimed at lowering β-amyloid levels in the brain and demonstrated measurable changes in tracer retention in response to treatment despite no clinical benefit [4, 5]. Although a positive β-amyloid scan has not yet been used as an inclusion criteria for these types of trials, future trials may require this, especially MCI and prodromal trials. Both small molecule and immunotherapy approaches are being pursued for PD and α-synuclein imaging would be invaluable for trials testing therapeutics aimed at lowering α-synuclein protein levels in the brain [6]. For example, the Austrian company, AFFiRiS, has a Phase I clinical trial underway to test an active immunotherapy approach in PD patients [7] and several other companies are approaching the clinic. In addition to directly targeting alpha-synuclein, a number of groups are pursuing disease modifying therapies which may indirectly lower alpha-synuclein levels [8, 9]. Despite the progress being made in getting these types of therapies to the clinic there are currently no good biomarkers for assessing efficacy within the timeframe limitations of a typical clinical trial. While α-synuclein can be measured in CSF and may ultimately prove to be a useful biomarker, the optimal assay conditions are still being developed and it is not clear yet how α-synuclein levels in the CSF relate to brain levels. A means of assessing α-synuclein in the brains of the patients would be a significant advance for these types of trials as well as other disease modifying approaches.

In 2011, MJFF assembled a consortium with the goal of developing a radiotracer that can be used widely by the research community as a biomarker of disease and disease progression, an outcome measure for clinical trials, and along with β-amyloid and tau tracers, a tool to investigate the relative contributions of different pathologies to clinical outcomes. The consortium members include a contract research organization, BioFocus, and two academic groups led by Robert Mach (University of Pennsylvania in collaboration with Washington University) and Chester Mathis (University of Pittsburgh). The consortium is working to develop a PET tracer with high affinity and selectivity for aggregated α-synuclein. While β-amyloid tracers were developed from conjugated dyes used in fluorescent staining of plaques and tangles in postmortem studies, these histological dyes tend to bind non-selectively to aggregated β-amyloid, tau and α-synuclein, although they tend to bind better to β-amyloid due to higher affinity and/or more available binding sites [10]. In order to identify molecules that bind selectively and with high affinity to α-synuclein, the consortium opted to take a small molecule, medicinal chemistry approach beginning with a screen of 100,000 compounds that were selected based on computational chemistry utilizing information derived from the α-synuclein structure. The screen utilized several assays that were developed by the consortium and identified novel lead compounds that bound selectively to α-synuclein. The consortium continues to optimize the lead compounds and to radio-label the most promising compounds for further development.

Developing an α-synuclein PET tracer poses a greater challenge than was faced for the β-amyloid tracers and in many ways is similar to the challenges faced for the development of a tau tracer [11]. Like tau, aggregated α-synuclein is far less abundant in the brain than β-amyloid and will therefore require very high selectivity for α-synuclein over β-amyloid and tau. Also, like tau, the majority of α-synuclein accumulates intracellularly, although some α-synuclein is found extracellularly either as a consequence of neuronal death or due to secretion from neurons and spreading in a prion-like manner [12]. Regardless, given that the majority of α-synuclein is found intracellularly, in addition to passing the blood-brain-barrier, a PET tracer would be required to cross the cell membrane, either by active transport or passively, in order to engage its target. While this is achievable, it introduces additional restrictions with respect to lipophilicity and molecular size.

Another important factor in determining the feasibility of developing an α-synuclein PET tracer is the density of binding sites in the PD brain. The density of binding sites must be sufficiently high to enable imaging with high affinity ligands. What little work
that has been done suggests that there should be sufficient binding sites on α-synuclein fibrils to enable in vivo imaging, with estimates in the same range as has been reported for tau, but perhaps an order of magnitude lower than reported for β-amyloid [13]. While these estimates represent a challenge for tracer development the challenge should not be insurmountable for a ligand with sufficient brain uptake, selectivity and affinity. Of note is that the density of binding sites for α-synuclein is substantially higher than many pre- and post-synaptic receptors for which PET tracers have been developed [14, 15]. Incidentally, α-synuclein is found in peripheral tissues such as the gastrointestinal tract as well but the quantities may be insufficient for imaging. Recent successes in the development of a tau tracer are also encouraging for the prospects for α-synuclein imaging. Tau tracers have advanced to human testing, with one promising tracer developed at Tohoku University School of Medicine and two others developed by Siemens Medical Solutions and recently acquired by Eli Lilly and being developed through their subsidiary Avid Radio pharmaceuticals. The newest tau tracer, PBB3, is being developed at the National Institute of Radiological Sciences in Chiba, Japan [16].

The identification of small molecules that bind selectively and with reasonably high affinity to α-synuclein fibrils from the initial screen is encouraging and ongoing optimization efforts should result in compounds that can be radiolabeled and tested in rodents and primates in the near future. MIF solders strategy is to test potential compounds in human pathological tissue as soon as possible to establish its relevance to PD and to move from initial in vivo studies in rodents and nonhuman primates to first in man studies quickly. The true test of the tracer will come from human studies given that no animal model faithfully recapitulates the human disease [17]. The time frame for developing a PET tracer can be a long one, on the order of several years, and requires some luck along the way. MIF seeks to accelerate this process through a concerted effort to combine resources and expertise from several different groups. MIF intends to make any successfully developed α-synuclein PET tracer widely available to the research community with the hope that it will benefit PD research and ultimately speed the development of new treatments for PD.

REFERENCES