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State of the Art

Imaging Biomarkers for CNS Drug Development and Future Clinical Utility: Lessons from Neurodegenerative Disorders

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ABSTRACT

Diseases of the central nervous system are common often chronic conditions associated with significant morbidity. In particular, neurodegenerative disorders including Alzheimer's and Parkinson's disease constitute a major health and socio-economic challenge with increasing incidence in many industrialized countries with aging populations. Recent work has established the primary role of abnormal protein accumulation and the spread of disease-specific deposits in brain as a factor in neurotoxicity and disruption of functional networks. A range of therapeutics from small molecules to antibodies targeting these proteinopathies are now in Phase 2 and Phase 3 clinical trials. These studies are methodologically challenging owing to difficulty of accurate diagnosis in early disease, the slow and variable rates of progression between individuals, and efficacy measures which may be cofounded by the symptomatic improvements due to treatment that does not reflect disease course modification. Further, the ideal candidates for these treatments would be at-risk, or premanifest persons in whom the pathological process of the neurodegenerative disorder has begun, but who are clinically normal and extremely difficult to identify. Scintigraphic imaging with PET and SPECT in trials offers the opportunity to interrogate pathophysiologic processes like protein deposition with high specificity. This review summarizes the current implementation of these imaging biomarkers and the implications for future management of neurodegenerative disorders and CNS drug development in general.

Key Words:
Positron emission tomography Drug development Alzheimer’s disease Parkinson’s disease

Introduction

Drug development for diseases of the central nervous system (CNS) has readily embraced the use of biomarkers as important tools for clinical therapeutic trials. The prime examples reflecting the most advanced use of biomarkers in CNS drug development, and of imaging biomarkers in particular, are in neurodegenerative disease. These represent a wide constellation of clinical syndromes reflecting for each disorder a characteristic pathophysiology and evolving pattern of changes in the brain. As a group, these disorders are common and generally encountered in older individuals in countries with aging populations. In Alzheimer's disease (AD), the most common of the neurodegenerative disorders, prevalence increases incrementally with advancing age. Data suggest individuals demonstrate cognitive impairment consistent with an Alzheimer's type dementia ranging from 5.3% of those ages 60-74 years to 34.6% of those ages 85 years and older(1). Aging is the greatest risk factor for developing AD, higher than high risk genotypes like apolipoprotein-E4 (APO-E4)(2, 3).

With these increasing numbers come greater demand for residential care and nursing services and concern about the capacity of health care systems to scale up. Costs associated with AD include nursing home care, physician visits, hospitalizations, and treatment as well as the more difficult to account for loss of productivity and uncompensated hours of care provided by family members(4). Recent health economics studies have focused on the high economic and social burdens on families caring for their afflicted member(5). Over the next 30 years the worldwide costs of caring for individuals with AD is estimated to increase by a factor of 10 (6). These observations are no less true for Parkinson's disease (PD), the second most common neurodegenerative disorder. Approximately 1,000,000 people in the United States carry this diagnosis representing a prevalence of about 0.3%. Again the disease is more common in elderly with rising incidence rates demonstrating in increasingly older cohorts(7). The estimated total economic costs posed by PD is expected to increase 52% to $79 billion by 2037(8).

These increasing social and economic burdens underscore the urgency to develop interventions that reduce the morbidity, delay the disease progression, maintain viable function and quality of life for as long as possible. The purpose of this review is to systematically explore the role of nuclear imaging in support of the development of these interventions, highlighting how the use of imaging has evolved as a crucial part of this therapeutic development endeavor, and how this informs future clinical nuclear medicine practice.

The Challenge of Developing Drugs for Neurodegenerative Disorders

These looming problems notwithstanding, the last twenty years have demonstrated significant progress in understanding the primary changes in the brain associated with neurodegenerative diseases(9, 10), focusing on therapies that may slow down, stop, or even reverse the disease course. Neurodegenerative diseases are primary disorders of protein deposition and distribution throughout the brain (TABLE 1). Common features of proteinopathies include the inexorable spread of aberrant protein species in intracellular and extracellular deposits leading to neuronal and/or glial cell death, the disabling of functional networks, and the emergence of clinical signs and symptoms reflecting this pathology(11, 12).

TABLE 1

The etiology of these disorders is largely unknown, however significant strides have been made toward characterizing the primary proteinopathy and course from the initiation of the disease process, through a clinically a silent phase of years duration, to first symptoms, and finally to full disease manifestation. (FIGURE 1). This knowledge informs therapeutic strategy including taking advantage of long, protracted period prior to overt symptoms as an opportunity to salvage significant function and potentially delay the onset of symptoms.

FIGURE 1

There are significant obstacles to translating knowledge of disease mechanism into effective treatments. Some of the problems result from the heterogeneity in clinical phenomenology with variability in symptom expression and progression rates. PD progression is slow and quite variable between patients. With such a slow rate of change rate in motor and non-motor symptoms, tracking even a 50% slowing of this change rate on a clinical assessment scale or motor score afterß a disease modifying intervention is quite difficult. This is especially problematic when clinical assessments are confounded by the salutary effect of symptomatic medications making it difficult to assess the baseline disease due to inability to completely wash out medications like l-dopa, even after two weeks withdrawal(13). The presymptomatic phase offers potential opportunity to intervene to delay or prevent manifest symptoms, but the problem is in identifying these presymptomatic or at-risk individuals.

Developing Imaging Biomarkers

Both imaging and non-imaging biomarkers may be of some utility in the clinical trial. Scintigraphic biomarkers using PET and SPECT have played different roles in multicenter clinical treatment trials in AD, PD, and other disorders. This includes demonstrating target engagement, aiding dosing determinations(14), enriching at-risk cohorts(15, 16), describing pathologic phenotype, serving as a gate-keeper for trial eligibility, assessing the natural progression of disease(17, 18), and evaluating the efficacy of a therapeutic intervention (19)(TABLE 2).

TABLE 2

Review of peer reviewed articles of studies in AD employing PET amyloid or tau shows strong growth in

the numbers of papers published annually from 2010 through 2021 (Figure 2 a-b). These data demonstrate the rapid development and implementation of amyloid PETß reflected in the early increased papers published and augmented several years later with the introduction of tau PET. This is consistent with clinical trial data for AD studies performed over roughly the past 7 years compiled in clinical trials.gov (Figure 2 c-d). This shows the relative proportion of PET targets in AD studies divided into “completed trials” or “recruiting trials”. For studies with the status of closed or completed the primary target was amyloid, while tau and other targets represent a larger component of recruiting projects. This suggests an evolving and expanding spectrum of imaging targets are being utilized in clinical trials.

FIGURE 2

Preliminary to its use in clinical trials, a biomarker itself needs to be validated, including understanding the relationship between the biomarker and the pathology it purports to measure (TABLE 3). For imaging biomarkers involving radiopharmaceuticals this process is comparable to standard drug development requirements for demonstrating safety and efficacy. Indeed, the amyloid and tau tracers served as biomarkers in multicenter AD trials with investigational therapeutics while concomitantly being developed for clinical use. This resulted in the unusual circumstance of two investigational drugs being utilized in the same trial, even as both were in early to mid developmental phases (20). While issues arose concerning how to assign adverse events to the appropriate drug, both development programs benefited. The investigational imaging agent greatly expanded its safety database and experience with real- world use of the radiotracer informing best protocols for acquisition and processing, and algorithms for visual reads. For the treating drug imaging enhanced the accuracy of the diagnostic cohort by setting eligibility requirements to a pathophysiology standard.

TABLE 3

Radiopharmaceutical development is similar to pharmaceutical development and subject to the same the pitfalls, scientific challenges, and regulatory requirements. However, unique to radiopharmaceutical development is the low mass dose of injected compound and hence the relative paucity of adverse events. The process of radiotracer development may be described as occurring in four stages: discovery, assessment, validation, and application (TABLE 4).

TABLE 4

Discovery is the process of investigating promising chemical structures that have a chance for high affinity and selectivity for the target as well as exploiting modifications to create a series of compounds with different the pharmacokinetics and pharmacodynamics. The original 11-C-labelled amyloid compound PIB amyloid was based on thioflavin-T and modified for in vivo use as a radiotracer(21). Certain target criteria regarding affinity, selectivity, and P- glycoprotein substrate status are initial goals for successful in vivo use. The introduction of highly efficient screening processes have greatly streamlined this aspect of development (22).

Assessment phase for radiopharmaceuticals requires the labelled compounds be produced with good

yields and high specific activity, have appropriate lipophilicity for brain penetration without decreasing signal-to-noise, have radiochemical stability, and upon injection shows high target uptake, fast washout of background activity, low off target binding, not a substrate for
P-glycoprotein, and no confounding metabolites.
Validation is characterization of in vivo pharmacokinetic properties evaluated in non- human primates or human Phase 1 trials(23). This stage checks the robustness and reproducibility of the outcome measure. This entails kinetic modeling of radiotracer distribution and developing quantitative measures (eg. distribution volumes or binding potentials (BP-nd)) and comparison with simple tissue ratio methods like SUVr, to understand the bias in the latter(24). This permits optimizing the acquisition protocol to minimize patient time in the camera (25). Radiopharmaceuticals must have a good safety profile with chemical toxicity, radiation dosimetry, and human studies evaluating adverse responses. All this in the service of providing an imaging outcome measure that is quantifiable, reproducible, reflects the pathology, and allows multiple scans over the course of a clinical trial.
Application refers to the use of the biomarker in clinical research trials. Specifically, logistical issues arise in getting high specific activity, GMP-produced radiotracer to the imaging site at adequate injected dose in a timely and consistent fashion. Distribution networks need to be established which optimize the greatest number of imaging centers being supplied by the fewest number of production centers and that these facilities can scale up to meet the needs of additional imaging centers onboarding. From the standpoint of the imaging, fewer imaging sites are better because PET technical standardizations is easier for creating a highly reliable pooled dataset across different studies sites. This may conflict with the recruitment needs of the trial which pushes for more clinical sites. One solution is to create a spoke and hub model where multiple clinical sites feed patients into a single imaging center.
Further, the service life of the PET camera must be considered given the long duration of these trials. The ideal is to image an individual on a single camera at baseline and follow-up scans and that those acquisitions are acquired in the same fashion and processed similarly to other scans in the study. Because of the different technical characteristics associated with cameras (reconstructed resolution, attenuation correction, sensitivity, etc) there will be differences. Fortunately, as the main outcome measure in most clinical trials (SUVr) is a ratio of target uptake to background and forgiving of issues such as sensitivity drift(26). Protocols for standardization of PET and MRI imaging biomarkers in the Alzheimer's Disease Neuroimaging Initiative (ADNI) was an early accomplishment of the study(27). Image quality assurance is managed by a rigorous site setup process where phantom studies and proscriptive image acquisition and processing protocols help standardize data.

Issues and Controversies

Imaging biomarkers in neurogenerative disease clinical therapeutic trials have dynamically changed over the last decade with the introduction of new radiopharmaceuticals, technical advances in instrumentation, more sophisticated image processing algorithms and outcome measures, and the thoughtful integration of different biomarkers into the clinical trial to achieve multiple ends (for example, eligibility and treatment efficacy). Some issues which highlight this development are the identification and optimization of radiotracers for protein deposition targets, quantitative and semiquantitative outcome measures, eligibility issues, and correlation, concordance and discordance of imaging with other biomarker and clinical assessments.

Target identification of protein deposition for tau is complicated by different tau isomers which create different structural brain deposits and for which tau radiotracers have different affinity (TABLE 5). This is an opportunity insofar as some radiotracers have higher affinity for the 4R isoform(28) and may be useful for eligibility assessment of PSP in clinical trials(29).

TABLE 5

Quantitative PET Outcome Measures

For quantitative assessment of PET/SPECT multicenter trials have relied on simple target to background brain tissue ratios like the standard uptake value ratio (SUVr) or the specific binding ratio (SBR, or SUVr-1). These have the advantage of being tolerant of camera sensitivity drifts, relatively easy to obtain, do not require blood sampling or arterial lines, and generally have robust test-retest reproducibility. However, the SUVr is a semi-quantitative measure which is affected by factors beyond the target site binding its purpose is to measure. These factors include hydration state of the patient, differences in metabolism, parent compound binding to intravascular plasma proteins; essentially anything that alters blood flow, delivery to, and washout of the radiopharmaceutical from the brain. Some have strongly argued that brain tissue ratios are misleading and should not be used for quantitation, while others advocate a compromise solution where at least some dynamic data with metabolite-corrected input function be acquired to assess the level and direction of bias posed by the SUVr(30). These studies should be in both the targeted population and controls to confirm the extent of under- or over-estimation the ratio. From a practical perspective, many imaging centers are unable to acquire dynamic scan data and/or sample and analyze arterial blood for generating an input function for kinetic modeling. Finally, the direct impact of the treatment on the chosen imaging outcome measure should be known. Does treatment affect the distribution or binding of the radiopharmaceutical to the target by means outside its purported mechanism of action for slowing disease progression? This is often addressed by a small human study in patients and controls done prior to the initiation of the large multicenter trial, sometimes in the context of a test-retest reproducibility study, to gauge the robustness of the chosen outcome measure.

Some large AD clinical trials have utilized different radiotracers for amyloid based on regional availability and needed a means to compare SUVr values between the different tracers. This is accomplished with the Centiloid conversion where a SUVr is converted to common Centiloid units which rescales the original SUVr based on the range of SUVr values from healthy volunteers to AD participants from 0 to 100 referenced against the PIB standard (31).

PET Visual Reads

For each radiopharmaceutical there is a unique pattern of uptake and brain distribution which can be understood and applied to an algorithm for visual interpretation of scans as either positive or negative or even with more granularity by assessing the extent and brain distribution of radioactivity consistent with an ongoing neurodegenerative process. This is best exemplified by the differences between the visual read methods for the tau PET radiotracers flortaucipir and MK-6240 wherein the former has a highly proscriptive algorithm for assessing temporal lobe positivity owing to the adjacent off-target

uptake obscuring mesial temporal structures.

As with other biomarker measures, a visual read needs to be validated for accuracy against some gold standard. This was a clinical diagnosis either by the site or by central expert panel agreement, rarely was pathology used for validating the imaging owing to the logistical difficulty in performing these postmortem studies. This changed with the commercial clinical development of the PET amyloid tracers, initially with florbetapir and followed by florbetaben and flutmetamol, all of which provided confirmatory postmortem evidence of the veracity of the amyloid PET scan in end-of-life participants compared to their own histopathology. This higher truth standard obviates some of the issues with clinical standards including the fact that in age-matched healthy volunteer groups scans may be abnormal in 20-30% in those age 65 years old and above. This population is the focus of a large multicenter clinical trial, the Anti- Amyloid Treatment in Asymptomatic Alzheimer disease (A4) Study which suggests those abnormal scans represent early AD and reflect the time lag between the onset of brain pathology and subsequent manifestation of symptoms(32).

Visual reads served as the major assessment for amyloid PET in a series of AD clinical trials and have been important in identifying potential research participants who do not have amyloid and are thus unlikely to have the disease targeted by the treatment. The rate of negative scans for participants sent for evaluation of brain amyloid burden runs from 10%-20% dependent upon the recruitment cohort with higher rates of negative scans in participants earliest in their disease course. This means that potential participants by all other measures are appropriate for enrollment, but that the amyloid PET suggests otherwise.

Ethical issues of appropriate disclosure to the potential research participant arise in instances of discordance between amyloid PET and the clinical team's diagnostic impression. The discordance falls both ways; clinical impression AD and amyloid PET negative, or clinical impression negative for AD and amyloid PET positive. The latter raises the delicate questions of a potential AD diagnosis and is addressed in clinical trials with educational materials, a detailed informed consent, and discussion with the clinical team during the consenting process (33).

Discordant interpretations of scans may also occur between the central core lab read and the site nuclear medicine read. Realistically discordance is low, approximately 3%- 4% of cases reviewed by local reader and the core lab readers. All readers are applying the radiotracer-specific read algorithm to their interpretations but for those difficult to interpret scans there may be more tendency of the core lab to bias toward negativity. Sites are under pressure to recruit and may be biased toward positivity and inclusion.

The central core lab and clinical site may run into discordance around diagnosis and eligibility for enrollment in the trials. Specifically, the imaging will sometimes show negative studies in a participant thought by the clinical team to have Alzheimer's dementia or Parkinson's disease. In Parkinson's the phenomenon of normal scans in potential participants for PD trial was given the name "scans without evidence of dopaminergic deficit" (SWEDD) designating them as not normal subjects without scintigraphic evidence of Parkinson's disease. When followed up longitudinally these patients' scans do not change, medication doses do not increase, and little clinical change occurs(34). The proportion of SWEDDs in a trial is related to the duration of symptoms with longer durations associated with fewer normal scans in putative PD subjects (Figure 3). This suggests the accuracy of the initial clinical

assessment may have been affected more in those with shorter disease duration, consistent with other studies of diagnostic accuracy in clinically uncertain suspected parkinsonism (CUSP) patients(35). These trials indicate that clinical diagnosis at enrollment overcalls PD relative to a one-year follow-up gold standard whereas the imaging is more accurate at the baseline assessment(36).

FIGURE 3

Correlation with Clinical Measures

Imaging biomarkers are secondary outcome measures to the primary clinical measure in therapeutic treatment trials. Complementary information from biomarkers may not align with with primary clinical assessments and correlations between imaging biomarker quantitative outcomes and clinical measures can be modest to poor. For example, in PD the correlation between specific binding ratios and clinical measures like the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) are poor at the onset of disease and with progression show moderate correlations (r= 0.30-.40) (37). This is because imaging biomarkers interrogate different aspects of the CNS than a clinical measure. The former provides a high specificity demonstration of a particular target; like amyloid, dopamine transporters, or other physiologic entity. Clinical outcomes are more downstream and represent the synthesis of the disease-affected output and compensatory networks. In a very dynamic system of a neurodegenerating brain correlation with clinical outcomes is different depending on when one measures the biomarker. This is not a weakness, but rather the purpose of utilizing complementary outcome measures, which can take advantage of these differences, as example, to use imaging to identify at-risk individuals prior to the manifestation of classic symptoms of the disease.

Complementarity and Integration of Biomarkers in Clinical Trials

It is not unusual for there to be several biomarkers, both imaging and non-imaging, which interrogate a single target. For example, one can determine amyloid positivity with amyloid PET, cerebral spinal fluid or blood assays, or retinal examination. For trial eligibility some studies now utilize hybrid approaches depending upon the availability of amyloid radiopharmaceuticals or CSF measures (a-beta 1-42) based on the high concordance rate between the measures (38) (Figure 4). Sometimes a biomarker best suited to the requirements of the study needs identification. These may be biomarkers within or between modalities, for example selection of an optimal tau PET agent for combined eligibility and disease monitoring or identifying the most sensitive way of detecting AD progression amongst PET and MRI measures like cortical thickness (39, 40).

FIGURE 4

In effort to address the need for validated imaging biomarkers for clinical trials, several large multicenter trials were developed to study the natural progression of disease in both Alzheimer's disease and Parkinson's disease. The Alzheimer's Disease Neuroimaging Initiative (ADNI) in the Parkinson's Disease Progression Marker Initiative (PPMI) are examples of such consortia. Both studies in their respective areas focus on the logistics of conducting standardized international multicenter multi-imaging modality studies in ways that provide for the highest standards of technical sophistication and

standardization across not only biomarkers but including other clinical measures. The success of these trials is measured by the influence on clinical trial design and the number of papers that have in developed with these data. Data are open access so that the academic and pharmaceutical communities can test hypothesis with data that they would have had to otherwise acquire themselves, with less efficiency, longer time to get results, and at greater expense. From a regulatory perspective, greater standardization of methods and analyses across different studies, different pharmaceutical companies, and different treatments allows for regulatory efficiency in the evaluation of proof of the safety and efficacy of the therapeutic.

Future Outlook and Relevance to Clinical Practice

The past five years has witnessed the evolution of an infrastructure and network of sophisticated clinical and imaging sites working in concert with radiopharmaceutical providers for the conductance of trials involving imaging biomarkers. Looking forward, one anticipates the further development of additional tracers with specificity for targets of interest, the extension of many of these techniques to other CNS abnormalities and finally a more intelligent and efficient use of imaging biomarkers in the conduct of both future research and future clinical care. There is a pressing need for biomarkers to interrogate alpha synuclein, the primary proteinopathy in PD(41). Recent advances include the alpha-synuclein seed amplification strategies for detection of the protein in CSF, saliva, and skin(42) and the preliminary human data in MSA patients with the putative a-syn PET tracer, ACI-12589. The role of other physiologic processes like inflammation, mitochondrial function, or the density of synaptic receptors are also of interest and are undergoing validation as PET radiotracers (43).

Imaging biomarkers have proven useful in clinical research, the algorithms and methods developed in these trials have potentially significant translatability to the practice of clinical care and nuclear medicine. Determining eligibility and appropriateness for a disease modifying therapy in clinical trials would be not too different in the clinical world at large. Specifically, the costs of many of these treatments may be high enough and having an imaging biomarker study performed prior to the treatment with the agent will be important to ensure that the disease for which the biomarker describes is positively noted on the scan. In addition, it remains to be demonstrated whether imaging can be used on an individual basis to assess the efficacy of treatment or imaging biomarkers alone or in combination with other assessments can predict the rate of progression for that individual patient.

Yet even as we look forward to the answers to these questions, the field has not as yet taken advantage of the synergistic use of biomarkers already in existence. The clever combination of fluid, genomic, clinical, and imaging and non-imaging biomarkers can result in more accurate characterization of phenotype, identification of at-risk individuals and better means for following and evaluating the effects of putative neuroprotective/neurorestorative agents as discussed. Of particular promise are efforts of accurate and early determination of a pathophysiological process like amyloid deposition, which if proving amenable to a disease modifying treatment, would make phrases like “Alzheimer's disease prevention” a reality and no longer an oxymoron.

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Noteworthy

1. Improved understanding of the basic pathophysiology of neurodegenerative disorders as brain proteinopathies provides new targets for treatment and biomarkers supportive of both clinical trials and clinical treatment.
2. The roles of biomarkers are varied depending upon the needs of the clinical trial including demonstration of target engagement, dosing determinations, cohort enrichment, diagnostic confirmation, disease monitoring, and clinical efficacy assessments.
3. As imaging biomarkers become routine in their clinical research use, they are defining their role in the clinic for routine management for those at-risk for and/or manifesting neurodegenerative disease.
4. Imaging biomarkers are a pathway to precision medicine supporting appropriate treatment across the spectrum of central nervous system disease.

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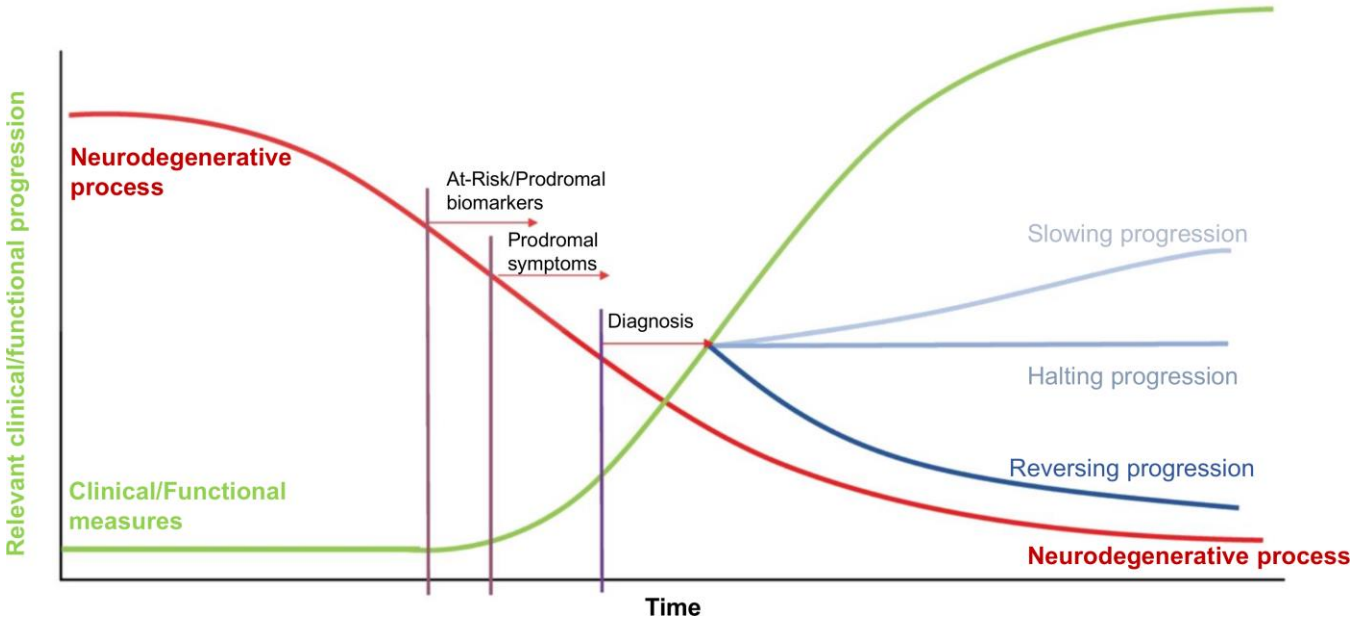

Figure 1. Model neurodegenerative disease time course. The neurodegenerative process is indicated in red as starting insidiously and remaining silent for years prior to manifest clinical symptoms (green line). Effects of interventions an the green curve are indicated by blue curves on the right, while diagnosis, prodromal symptoms, and at-risk assessment period tied to the pathophysiology suggest imaging biomarkers may be changing years before clinical symptoms. Adapted with permission from (47)

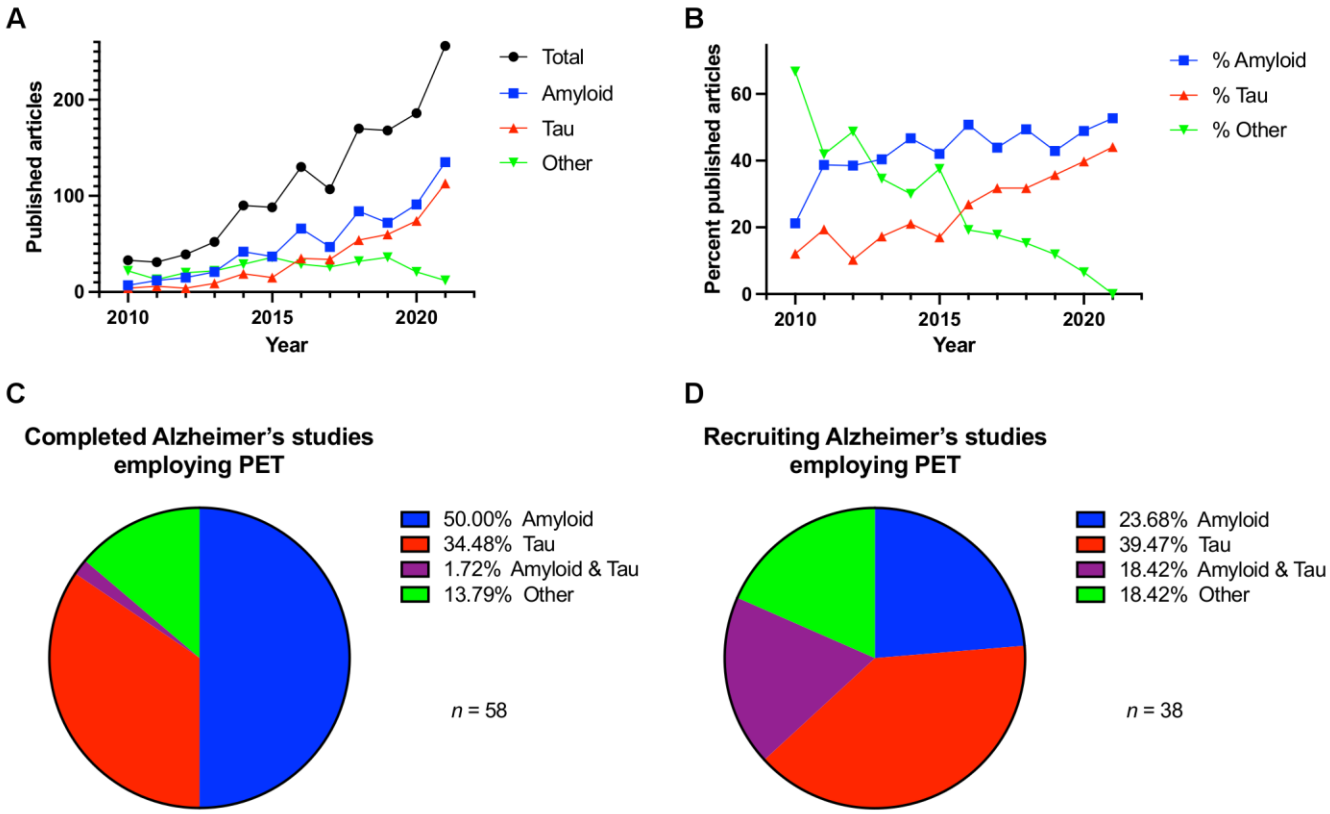

Figure 2. Number of papers in neurodegenerative disease published between 2010 and 2021 where PET imaging was performed (panel A). These were largely amyloid and later tau studies. Panel B shows the data expressed as a percent showing the high percentage of amyloid PET studies with tau PET coming in the last 5 years. Source: Pub-Med. Bottom panels show percent breakdown of PET radiopharmaceuticals for amyloid and tau in AD for studies with a status "completed" or "recruiting" (C and D, respectively) demonstrating more recent focus on tau in the research activity. Source: clinicaltrials.gov.

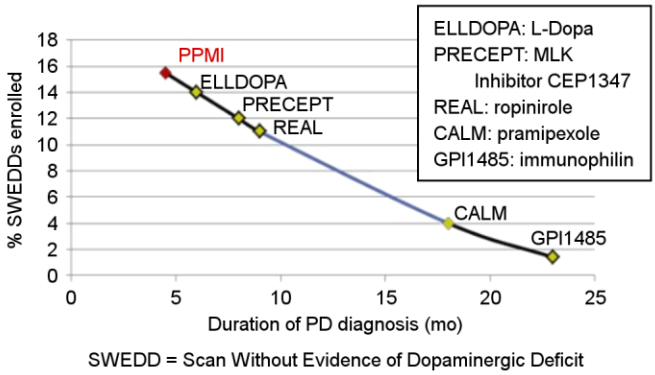

Figure 3 Percentage of normal scans in early PD trials for patients with clinical diagnosis of Parkinson's disease demonstrate at earlier time points post symptom presentation the percentage of the dopamine transporter SPECT scans known as SWEDD increases. Diagnostic certainty improves with greater duration of illness. Adapted with permission from (48)

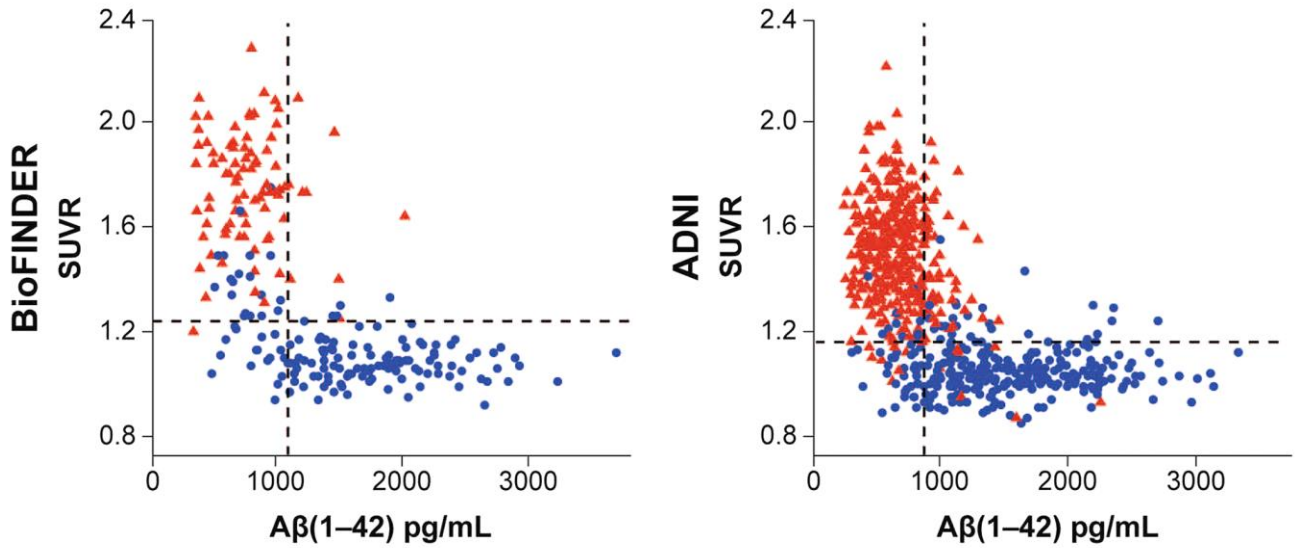

Figure 4 Correlation between PET amyloid SUVr and CSF measures of a-beta (1- 42) in the BioFinder study and ADNI. Red triangles indicate positive scans on visual read, while blue circles are negative on visual read. There is an inverse correlation between PET SUVr and CSF a-beta in both studies. From (38) Hansson, et al. J Alzh Dementia, 2018 Used with permission granted by author reuse and cc license policies.

Table 1. Key Clinical Features and Primary Pathology in Neurodegenerative Disorders

Disease	Key Clinical Features	Pathology
Alzheimer's disease	Progressive memory loss	ß-Amyloid, Tau (3R,4R)
Parkinson's disease	Tremor, rigidity, bradykinesia, gait disturbance	Alpha-synuclein
Progressive supranuclear palsy	Motor disturbance, gaze palsy	Tau (4R)
Multiple system atrophy	Autonomic dysregulation, motor disturbance	Alpha-synuclein
Dementia with Lewy bodies	Memory loss, motor disturbance, hallucinations	Alpha-synuclein
Chronic traumatic encephalopathy	Variable cognitive, behavioral, mood and motor changes.	Tau (3R,4R)
Corticobasal degeneration	Akinesia, rigidity, dystonia, disequilibrium	Astroglial plaques and tau (4R)
Huntington's disease	Affective lability, choreiform movements, memory loss	Mutated huntingtin protein (mHtt)
Amyotrophic lateral sclerosis	Progressive loss of voluntary muscle control	TDP-43 proteinopathy (SOD1, FUS variants)
Down's syndrome	Intellectual impairment, subsequent memory loss	ß-Amyloid

Table 2. Roles of Imaging Biomarkers in Drug Development

Role	Study Phase	Example
Showing target engagement	Phase 0	D1 MNI800, MNI968
Aiding dosing determinations	Phase 1	DISPLACEMENT(44)
Enriching at-risk cohorts	Phase 2, 3	PARS STUDY (17)
Describing pathologic phenotype	Phase 2, 3	AVID AV1451 (45)
Serving as a gate-keeper for trial eligibility	Phase 2, 3	A4 Trial (32)
Assessing the natural progression of disease	Phase 3	ADNI, PPMI (46)
Evaluating the efficacy of a therapeutic intervention	Phase 3	BIOGEN ADUCANUMAB

TABLE 3. Expected Imaging Findings in Neurodegenerative Disorders

Disease	Amyloid	Tau	A-Synuclein	DAT
Alzheimers	Increased	Increased	NL	NL
Idiopathic PD	NL	NL	Increased	Decreased
Dementia Lewy Bodies	NL or Increased	NL	Increased	Decreased
Multiple System Atrophy	NL	NL or increased	Increased	Decreased
Older healthy volunteer	NL or Increased	NL	NL	NL
Progressive Supranuclear Palsy	NL	Increased	NL	Decreased
Essential Tremor	NL	NL	NL	NL
Drug-induced PD	NL	NL	NL	NL

Table 4 Development of Imaging Biomarkers for Clinical Trials

Stage	Activities	Benchmarks
Discovery	Identify candidate structures In vitro testing for best compounds Optimize radiolabeling	Good yield, high specific activity, stable
Assessment	Affinity	Postmortem Human Brain Homogenates or sections Ki <1 nM
	Selectivity	>200 fold selectivity
	Lipophilicity	Log $D_{7.4}$ = 2 to 3.5
	Stability	4 half-lives
	BBB	P-glycoprotein substrate (MDR1-MDCK)<20
	Metabolite Identification	Ex-vivo analysis (characterize all major metabolites with a radiolabel)
Validation	Correlation and Safety	High Signal:noise Correlation w/ histopath Correlation w/ clinical Dosimetry
	Quantitative accuracy	Full kinetic modeling including arterial input function corrected for metabolites Streamline protocol for clinical use Test-retest of all outcome measures
Application	Logistical feasibility	Production/distribution network Imaging site technical standardization

TABLE 5. Some Tauopathies and their Brain Targets

Disease	Tau lsoform	Primary pathology	Brain localization	Regions with highest PET uptake
Alzheimer's	3R,4R	Paired helical filaments	Cortical	Temporal, post cingulate
Progressive Supranuclear Palsy	4R	Straight filaments	Subcortical	Globus pallid., putamen,sub n.
Corticobasal degeneration	4R	Straight filaments	Subcortical	Globus pallid., putamen
Chronic traumatic encephalopathy	3R,4R	Paired helical filaments	Cortical	Frontal, temporal, diencephalon
Down's	3R,4R	Paired helical filaments	Cortical	Temporal, post cingulate