Cleveland Clinic Lou Ruvo Center for Brain Health
Neurological Institute
Cleveland Clinic

THE RELATIONSHIP BETWEEN NEUROPSYCHOLOGICAL TESTING AND MRI, PET AND BLOOD BIOMARKERS IN NEURODEGENERATIVE DISEASE (NIH): AIM 2

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ABBREVIATIONS

AD	*Alzheimer's disease*
AE	*Adverse Event*
BAA	*Business Associate Agreement*
CNTN	*Center for Neurodegeneration and Translational Neuroscience*
COBRE	*Center of Biomedical Research Excellence*
DRS	*Dementia Rating Scale*
eCRF	*Electronic Case Report Form*
FDA	*Food and Drug Administration*
GE180	*(S)-N,N-diethyl-9-(2-[18F]fluoroethyl)-5-methoxy-2,3,4,9-tetrahydro-1H-carbazole-4-carboxamide ([18F]GEH120714) also known as Flutriciclamide (^{18}F-GE180) an experimental PET tracer*
ICMJE	*International Committee of Medical Journal Editors*
IRB	*Institutional Review Board*
MCI	*Mild cognitive impairment*
MoCA	*Montreal Cognitive Assessment*
MRI	*Magnetic Resonance Imaging*
MTA	*Material Transfer Agreement*
PD	*Parkinson's disease*
PET	*Positron Emission Tomography*
SAE	*Serious Adverse Event*
TSPO	*Translocator Protein*
UNLV	*University of Nevada, Las Vegas*
UP	*Unantcipated Problems*

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1. Background and Significance

This is a research study that will evaluate imaging characteristics of a PET tracer named GE180 that indicates regional neuroinflammation in cognitively normal older adults, patients with mild cognitive impairment, and those with Parkinson's (PD) or Alzheimer's disease (AD). All participants will be part of a registry from the Center for Neurodegeneration and Translational Neuroscience (CNTN), which provides a well characterized pool of participants with the aforementioned diagnoses.

Inflammation has been shown to be part of the early pathogenic mechanism of AD[1] and PD[2], and represents an important potential target for therapy. These two diseases have distinct patterns of cognitive dysfunction, especially early in the disease course. In AD, amyloid depositions occur early in the disease process and by the time clinical symptoms are evident, are diffuse in the brain, while the spread of tau pathology in the brain occurs in a predictable topography, with spread from the medial temporal regions early in the disease to the association cortices of the frontal and parietal lobes as the disease progresses. This topographical distribution is closely associated with specific cognitive changes, which can be tracked with neuropsychological tests. The spread of disease-specific proteins in PD is less well understood, but there are particular cognitive trajectories that can be followed. Inflammation has also been shown to play a role in these disorders. If inflammation is a common element which can be visualized and quantified regionally, and is associated with particular cognitive dysfunction, then this would (a) demonstrate a target of therapy which may not be disease specific and (b) identify a way to measure the impact of any intervention.

Microglia are the central nervous system's phagocytes, and are distributed throughout the brain. They are very active and, in addition to an anti-inflammatory role, they have a role in plasticity and remodeling of synapses[3]. GE180 is an experimental PET tracer that binds to a mitochondrial translocator protein (TSPO), which is produced by microglia and is a putative biomarker for inflammation. TSPO is minimally expressed in the CNS in humans when healthy, but dramatic increases are apparent in response to neuronal damage and inflammation[4]. There have been some human studies with GE180 already[5] and it is similar to an earlier experimental tracer ^{11}C-(R)-PK11195 which has been tested more exhaustively over the last 20 years[6]. GE180 has been found to be superior to ^{11}C-(R)-PK11195 due to stronger signal to noise ratio and different pharmacokinetic properties including longer half-life[7]. Animal studies have shown GE180 to detect both AD-related and age-related changes in mice[8]. Several studies are currently underway in the UK, Canada and the USA using GE180 in disorders including AD and PD. To our knowledge, none of these studies uses as in depth cognitive profiling as will be used in the current study.

Early research with a more primitive PET tracer ^{11}C-(R)-PK11195 revealed that AD patterns of inflammation were suggestive of regional change and associated with reduced cognition as assessed using a nonspecific measure[9] . In PD, two different patterns emerged, one being more general, the other more specific to certain cortical regions. This early research did not take advantage of neuropsychological methods which might elucidate the specific cognitive change

seen in these two diseases. By applying these methods, we hope to gain a far deeper understanding of the relationship between microglial activation and cognition across these two diseases.

1.1 Purpose

The purpose of the study is to assess the relationship between (a) overall and (b) regional inflammation with (a) overall and (b) domain-specific cognitive function in AD and PD. If we demonstrate a correlation between regional uptake of GE180 and specific cognitive profiles, further research will be warranted to investigate whether therapeutically driven reduction in inflammation also leads to improvement in cognition.

2. Study Objectives

The overall objective is to establish the relationship between regional microglial activation and neuropsychology test scores in patients with diagnoses of Alzheimer's disease and Parkinson's disease.

We will test the hypothesis that regional enhancements in microglial activation would be reflected in neuropsychological test scores: The degree of memory impairment would be related to medial temporal lobe microglial activation, visuospatial impairment would relate to more posterior activation, executive dysfunction would relate to frontal activation. We will also test the hypothesis that higher levels of global inflammation will be associated with more severe cognitive impairment, especially in patients with mild cognitive impairment.

3. Study Design

This study will involve a cohort that is currently being established at the Cleveland Clinic Lou Ruvo Center for Brain Health. The cohort has been established under the NIH Center of Biomedical Research Excellence (COBRE) grant and involves annual collection of detailed neuropsychological and biomarkers (blood and neuroimaging) from all participants annually. Data are filed in a registry (CNTN). Under a data sharing agreement, all neuropsychological, blood screening, MRI, and PET data from CNTN will be available to Dr. Ritter (who is also a Clinical Core Leader on the COBRE project). Participants include healthy participants, participants with PD (with and without mild cognitive impairment (MCI)) and patients with MCI (with or without positive florbetapir scan, which demonstrates underlying AD changes likely causing the cognitive impairment) and patients with AD. For the current study, we will focus on patients with MCI with associated underlying AD or PD.

Participants will undergo GE180 PET. Our approach to PET data collection and analysis will be similar to work done previously with an earlier generation ligand [10] and to other work with this tracer[5]. We will complete ECGs prior to and immediately following injections. Briefly, the ligand will be injected, scan acquisition will then begin and will be collected in list mode and rebinned into 18 time frames post acquisition.

The total duration of the study will be around 2 hours, and the participants will receive $50 compensation for the visit.

4. Population

A total of 70 participants will be recruited from the CNTN cohort. Specifically, we will recruit 10 healthy participants, 20 MCI (10 of whom will be florbetapir positive, and 10 florbetapir negative), 20 AD patients and 20 PD patients, 10 of whom will be cognitively intact and the other 10 will meet criteria for MCI. Participants will be age matched and they will be extracted from the larger CNTN cohort which stratifies to race based on the Nevada data from the 2014 US Census.

4.1. Inclusion/Exclusion criteria

Inclusion criteria

1. Be enrolled in CNTN
2. Aged 55 to 90
3. Available study partners
4. For MCI patients, fit criteria based in Movement Disorders Task Force or NIA

Exclusion criteria

1. Significant neurological disorders other than AD or PD;
2. Unstable medical conditions
3. History of major psychiatric diseases
4. MRI evidence of infarction or other focal lesion or multiple lacunes
5. Clinically significant abnormalities in B12 or TSH
6. Identified as having a common polymorphism (rs6971) in the TSPO gene which has been shown to reduce binding affinity of tracers similar to GE180[11]. This testing will be done as part of their CNTN participation.

In addition, subjects must answer questions in regards to their history of radiation exposure over the past year (past 12 months to day of screening). If their radiation exceeds half of the recommended amount (any amount greater than 25 mSv), they may not participate at the present time. However, assuming they are eligible against all other inclusion/exclusion criteria, they may be eligible for a scan in the future once their 12 month exposure is less than half of the recommended amount.

4.2 Subject recruitment

All participants will be recruited via the CNTN cohort.

4.3 Subject screening

All subjects who are part of the CNTN will be eligible for participation in the current study, other than those carrying a known genetic polymorphism, TSPO rs6971 polymorphism which impacts binding of GE180 and other TSPO binding agents, which occurs in approximately 10% of the

population. We will not recruit patients with this polymorphism. Since they will have already been followed in CNTN we will have this data prior to recruitment.

5. Study Procedures

The below procedures will be completed on all participants:

4.1 Recruitment at CNTN Study Visit

The CNTN has been collecting data since mid-2016. We will recruit participants as they come for their follow-up visit. Suitable participants will be made available for the study by the CNTN staff if they agree for data to be shared with this study. At that point, study staff will contact the potential participant and conduct a brief screen over the telephone or in person, explaining the content of the current sub-study. If the potential participant demonstrates interest and willingness to continue, they will be asked to come in to discuss informed consent at their next CNTN visit. We will recruit patients into each cohort from the CNTN, at which point they will already have been characterized with neurology, neuropsychology and neuroimaging (amyloid PET and MRI) as well as having blood work completed. CNTN participants will be invited to recruit in the current study at their CNTN visit.

4.2 Consent Visit

This could potentially happen on the same day as the CNTN visit, in order to reduce the number of study visits. Participants will be given time to review the materials with their study partner, and then with the coordinator who will allow them to ask any questions they may have. Once fully informed written consent is obtained by both the patient and their study partner, the baseline GE180 PET visit will be scheduled.

4.3 PET

The participants will come for their visit, have their vitals and ECG taken, and will have fresh blood samples drawn. GE180 will then be injected and the scan will be performed. They will then have a secondary ECG. After this they will be free to leave. They will receive a wellness phone call from the study coordinator 48-72 hours later. The coordinator will stop making attempts to reach the participant after three unanswered calls.

6. Data analysis

Study size determination was completed using another previously published study [12] that used an earlier generation microglial ligand. Based on binding potentials in the same region (anterior cingulate cortex) we calculated that at a significance level of .05, and in order to attain a correlation of r=.8 we would require 10 subjects for 90% power in analyses of microglial activation from each of the regions of interest and the key cognitive outcome measures. Given that we are using a different ligand and will be looking at more regions, we have increased the number so we can be confident in our results. It is important to note that sample size calculations based on neuroimaging

data are limited, but the numbers proposed here are similar to or in excess of other studies using and novel PET ligands [10], thus we predict that the group sizes will be sufficient.

Data Analysis will be conducted by the study team under the direction of the Principal Investigator.

Image analysis will be conducted using parametric analytic technique in SPM12, combining GE180 results with the participants' own MRIs. This will allow us to compare individuals in each disease group with an averaged image of controls. In addition, we will be able to extract uptake values in regions of interest to compare across groups and in relation to test scores. This approach is being used by colleagues at another site that is currently studying GE180 in older adults.

Microglial activation data from each of the region of interest (ROI), in addition to overall cortical load, will be extracted. It will be represented statistically as a function of cortical thickness in that region. These data will be used in two analytic steps: the first using measures of overall cognitive function (assessed with the Dementia Rating Scale (DRS) and Montreal Cognitive Assessment (MoCA)), and the second using key cognitive outcome measures specific to the domains of memory, visuospatial function, language and executive functioning. These measures are all collected as part of the CNTN. We will use a linear regression model to assess whether regional microglial activation predicts cognitive performance. We will also complete repeated measures analyses to assess whether there is a change in microglial activation between time points and, if so, if this relates to changes in the cognitive measures.

6.1 Predicted outcome: At baseline, we expect to find overall cortical load of GE180 uptake to predict summary scores on the DRS and MoCA, and for regional loads to predict specific cognitive domains. In PD-MCI we expect more cortical enhancement than in the PD-NCI subjects. Specific expectations across disease states include that hippocampal and temporal cortex load will be related to memory, frontal cortex load to executive ability, parietal load to visuospatial ability. We also expect baseline levels of microglia to predict future decline in cognition but there will not be an increase in microglial activation over time. This final expectation is based on data collected with the earlier generation microglial ligands, but change over time is yet to be explored in humans with GE180.

7. Study Drug

7.1 Investigational Agent

GE180 is a PET imaging agent which was developed as a non-invasive *in vivo* probe of neuroinflammation. The mechanism of action is based on its high affinity for TSPO and high selectivity, with little binding to other receptors, transporters and channels. TSPO is elevated in response to neuronal damage and inflammation, such as occurs in neurodegenerative disease. *In vitro* studies support GE180's high affinity to TSPO and high selectivity, with little binding to other receptors, transporters and channels.

7.2 Preclinical data

Nonclinical pharmacology data of GE180 supports its potential use to visualize TSPO *in vivo*. In preclinical models of stroke and inflammation, GE180 has been shown to be effective in detecting

inflammation in animal brains[7,13]. Specifically, in mouse models of normal aging and AD, Liu and colleagues found a clear association between GE180 uptake and amyloid plaques, as well as immunohistochemical co-localization of GE180 and other microglia markers. They also showed an age-dependent elevation in whole brain uptake consistent with the notion that both aging and AD pathogenesis involve increased inflammation[8].

7.3 Clinical data to date

Human studies of early inflammatory markers were hampered by reduced binding affinity[14] and difficulty distinguishing the signal from noise related to uptake in the endothelial cells of the blood brain barrier and venous signal[15]. It was hoped that GE180 would counteract these problems and enhance the visualization of neuroinflammation in humans. Several clinical studies are currently underway. The first publication of human research has been focused on methodology[5]. Fan et al used 15 healthy adults aged 50-85 years. Their study was used to optimize scan length and to investigate the feasibility of generating parametric maps using graphical analysis. Results from their study have been incorporated into the design of the current study.

7.4 Dose rationale

GE180 is an intravenously administered diagnostic radiopharmaceutical used for PET. It is formulated as a clear, colorless aqueous solution containing NMT 10.0% v/v ethanol in phosphate buffered saline (PBS) with a pH of 6 – 8. It contains 90 – 110% of the labelled amount of ^{18}F expressed as MBq/mL. There are no preservatives. It is manufactured to GMP standards and is supplied in a sterile endotoxin-free 10 mL glass vial. Study participants will receive a standard dose of 185MBq with maximum radioactivity dose of 270 MBq in a maximum volume of 10 mL (bolus) of GE180, containing not more than 2 μg/mL GEH120714 (20 μg for a 10 mL dose).This is consistent with other sites using the tracer.

7.5 Preparation and Administration of Study Drug

GE180 will be manufactured as a radiolabeled drug product by Banner Health in Phoenix, Arizona, a health center that also specializes in the manufacturing and distribution of radiopharmaceuticals, with individual unit dosing through its own radiopharmacies and cyclotron-based PET manufacturing facilities. Using a GE FASTLab synthesizer with disposable cassettes (manufactured by GE Healthcare AS in Oslo, Norway), Banner will produce individual doses. Individual doses will be delivered to the Cleveland Clinic via Banner immediately after production. Administration will be similar to that already performed in humans. We will administer 185 MBq by bolus intravenous injection (in 20 seconds) immediately before the PET. All scanning will be completed on the PET scanner. An initial CT will be acquired for patient position and for attenuation correction of the PET images. The tracer will be injected and dynamic emission PET images will be acquired over 30 minutes 90 minutes post injection as shown to be optimal GE. The imaging protocol will be as follows:

Method: Iterative: OSEM-3D (do NOT use TrueX or ToF reconstruction) 4 iterations; 24 subsets
Grid: 400 × 400 × 81 (or 109 for TrueV model)
Zoom: 2.0 (results in voxel size of ~1.018 mm)
Smoothing Filter: NONE (All-pass or '0.0')
Match CT: 'Off' or 'No' (results in PET slice thickness of ~2.027 mm)
All corrections 'On'

Images will then be corrected for attenuation, random and scattered emissions based on the 3D.

7.6 Receipt of Drug and Storage

Doses will be requested from Banner Health one week prior to need. Details of drug ordering, receipt and use will be kept on a log onsite and completed by designated study staff. These staff will verify that the dose is delivered intact, to the best of their ability. Any apparent discrepancies will be reported to the PI and Banner Health immediately, and the dose will not be used.

GE180 will be stored upright in a lead shielded container at 15 – 30^{o}C.

8. Data management

All participants will be assigned a unique study-specific ID when enrolled. Data will be housed in a Part 11 compliant database being created with OpenClinica. This same database will also house all COBRE data which will be available to Dr. Ritter his role as Core Leader on that grant-sponsored project. Data will be entered by Dr. Ritter or his delegate, and both will be trained in the handling sensitive patient data.

8.1 Records Retention

Records will be retained for at least 6 years following the termination of the study. Records will be retained digitally on secure servers and paper documents will be secured in locked cabinets with access limited to study staff.

8.2 Blood Samples Analyses

Neuroinflammation is increasingly identified as a key driver of neurodegeneration. However, current studies typically use peripheral blood to identify evidence of neuroinflammatory processes. These have not been correlated with changes in the central nervous system.

We will draw blood markers of inflammation to correlate with changes seen on GE180. Inflammatory markers will be collected, stored, and analyzed at UNLV by Jefferson Kinney, Ph.D who is covered under an existing Business Associate Agreement (BAA) with LRCBH.

On the day of the scan, these samples will be picked up by a member of the UNLV team to be processed and stored. Samples will be picked up within two hours of blood draw. The de-linking of the sample from the participant's PHI occurs at the time of collection at LRCBH. The identity of participants will not be shared with the UNLV team. The participant's identification number will be affixed to the specimen tubes along with date of blood draw. LRCBH will maintain a database for tracking all samples into the CTRC that will include the following information: study ID number, date of collection, cohort, age, gender. All clinical data will be de-identified and study personnel outside Cleveland Clinic will not have access to the data key. Biospecimen management for sample receipt, processing, and analysis, has been approved by the UNLV Institutional Review Board and the stored specimens will be in accordance with the rules and procedures established by the UNLV IRB.

Additional samples may be sent to other collaborators provided that an approved Material Transfer Agreement (MTA) is put into place between this institution/individual and LRCBH. The same de-linking process as described above will be utilized in these cases. After the de-identified sample has left LRCBH, it is the responsibility of the outside institution/individual and their IRB to develop approved protocols and procedures detailing the usage and storage of these samples.

9. Safety Monitoring

PET brain imaging with GE180 entails no more than minimal risk per the Investigator Brochure.

Monitoring of this study will occur through the Cleveland Clinic Coordinating Center for Clinical Research, the details of which are provided in the attached Monitoring Plan.

A Data Monitoring Committee will not be used to review safety data involving adverse advents for this study as all study procedures can involve no more than minimal risk.

9.1. Ethical considerations

This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to the Cleveland Clinic Institutional Review Board (IRB), for formal approval of the study conduct. The study will be monitored according to the attached

Monitoring Plan. No study recruitment will take place until FDA IND approval has been obtained, and the IRB has approved the study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision

9.2. Privacy

Patient data will be analyzed in a completely de-identified format in order to minimize any risk to patient privacy. Information about study subjects will be kept confidential and managed according to the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Subjects or a legally acceptable surrogate will provide authorization that they have been informed of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke authorization for use of the PHI.

The HIPAA language is included as part of the informed consent form.

Any electronic data will be maintained on secure servers behind the Cleveland Clinic firewall and on the OpenClinica database as outlined above. The database will be populated by the study research coordinator.

The study CRFs have been constructed for this study. All data will be collected on the CRF and all missing data on the CRF will be explained.

All documents will be retained for a minimum period of six years following completion of the study.

9.3. Adverse Events and Data Monitoring Committee (DMC)

Due to the minimal risk of the study procedures the likelihood of adverse events is very low. No data monitoring committee will be employed for the study. Adverse events (AE) will be evaluated by the P.I. and reported to the Cleveland Clinic IRB for review according to the AE reporting protocols set forth by the IRB. FDA guidelines will also be followed in reporting adverse events. Unanticipated problems (UP) will be reported as soon as they occur to the IRB.

No clinical report will be generated from the testing completed as part of this study.

9.4. Informed consent procedures

After detailed explanation of the study and its potential risks, informed consent will be obtained by a member of the study team prior to commencement of scanning. The informed consent process will be documented in the research record. A copy of the signed informed consent form will be provided to the participant and the original signed form will be stored in the research record.

10. Publication of study protocol and results

Upon study completion and finalization of the study report, the results of this study will be presented at appropriate scientific meetings and published. Publications will comply with the standards of the Cleveland Clinic Foundation and the International Committee of Medical Journal Editors (ICMJE) guidelines.

The study will be registered on ClinicalTrials.Gov and results will be reported there.

11. Study Monitoring, Auditing and Inspecting

11.1 Study Monitoring Plan

This study will be monitored under the Cleveland Clinic Coordinating Center for Clinical Research. Monitoring activities will be carried out according to the monitoring plan (see attached). The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (for example, PET scanning suite), and has adequate space to conduct the monitoring visit.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and Institutional compliance and quality assurance groups of all study related documents (for example, source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (for example, PET scanning suite). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Institutional compliance and quality assurance offices.

12. Study Finances

12.1 Funding Source

This study is funded through a grant from the National Institute of General Medical Sciences grant number 5 P20 GM109025-02.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain) must have the conflict reviewed the by Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All Cleveland Clinic investigators will follow the Institutional conflict of interest policy. Each Investigator will complete a Cleveland Clinic specific Financial Disclosure Form per Institution requirements.

12.3 Subject Stipends or Payments

Subjects will be paid $50 compensation for the study visit.

13. Publication Plan

Dr. Ritter and Dr. Caldwell, Co-Principal Investigators, have primary responsibility for publication of the results of this study. It is the full intention of the investigators to publish the results of this study as soon as possible.

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