DISCOVERY OF [18F]ACI-12589: A NOVEL AND PROMISING PET-TRACER FOR ALPHA-SYNUCLEIN

Francesca Capotosti, PhD | AD/PD™ 2022 | 18 March
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Disclosures
Francesca Capotosti is an employee of AC Immune entitled to stock options

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A-syn\(^1\) PET\(^2\) tracers can improve the diagnosis and treatment of NDD\(^3\)

An effective PET tracer is needed to best enable precision medicine for α-synucleinopathies

- Early Diagnosis and Treatment is Key in NDD
- Early diagnosis of α-syn-opathies\(^4\) is not possible with current techniques
- Benefits of PET tracers for imaging have been validated

- Once neurons are damaged, they cannot be repaired or replaced with current therapies
- Dopaminergic imaging correlates poorly with disease severity
- Genetic testing is ineffective in most cases
- Low abundance of α-syn limits utility of fluid biomarkers
- Patient stratification
- Better clinical trials when focused using PET tracer for recruitment and monitoring
- May enable combination treatment of co-pathologies

(1) Alpha-synuclein; (2) Positron emission tomography; (3) Neurodegenerative disease; (4) Alpha-synucleinopathies
Precision medicine approach enabled by the Morphomer® platform

Developing a suite of PET\(^1\) tracers against emerging targets in NDD\(^2\)

Leverage the Morphomer® small molecule platform:

- Non-peptidic, small molecules with CNS-drug properties for brain penetration
- Conformation-specificity (pathologic protein species)
- Selectivity against co-pathologies (Abeta, Tau, TDP-43)
- Pharmacokinetics suitable for brain PET imaging

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(1) Positron emission tomography; (2) Neurodegenerative disease; (3) Neurofibrillary tangles; (4) Alpha synuclein; (5) TAR DNA binding protein-43
ACI-12589: a potential a-syn\textsuperscript{1} PET\textsuperscript{2} tracer

[\textsuperscript{3}H]ACI-12589 specific binding on brain tissue from different a-synucleinopathy cases

- ACI-12589 displays a clear autoradiography signal which correlates with the presence of pathological a-syn
- Binding affinities are measured in the range of 8-30 nM with Bmax/Kd ratios of ~ 5-10

(1) alpha-synuclein; (2) Positron emission tomography; (3) Parkinson’s disease with G51D SNCA mutation; (4) Multiple system atrophy; (5) Immunohistochemistry
ACI-12589: a potential a-syn\(^1\) PET\(^2\) tracer

[\(^3\)H]ACI-12589 target engagement on a range of different a-syn inclusions

- ACI-12589 displays strong target engagement on Lewy bodies and Lewy neurites, as well as smaller a-syn inclusions, across a wide range of a-synucleinopathies

(1) alpha-synuclein; (2) Positron emission tomography; (3) Parkinson’s disease; (4) Parkinson’s disease with dementia; (5) Multiple system atrophy; (6) Dementia with Lewy bodies; (7) Lewy body variant of Alzheimer’s disease; (8) Immunohistochemistry

Ref.: Capotosti et., AAIC 2020
ACI-12589: a potential a-syn\(^1\) PET\(^2\) tracer

[18F]ACI-12589 specific binding on brain tissue from different a-synucleinopathy cases

- Familial PD\(^3\)
- PDD\(^4\)
- PD\(^5\)
- MSA\(^6\)
- LBV\(^7\)

- Healthy Controls

Classical autoradiography experiments confirms specific binding across a wide range of a-synucleinopathies

- (1) alpha-synuclein
- (2) Positron emission tomography
- (3) Parkinson’s disease with G51D SNCA mutation
- (4) Parkinson’s disease with dementia
- (5) Parkinson’s disease
- (6) Multiple system atrophy
- (7) Lewy body variant of Alzheimer’s disease
- (8) Immunohistochemistry
ACI-12589: selective versus Abeta and Tau

[3H]ACI-12589 assessed using Alzheimer’s disease tissue

Radiobinding with AD\(^1\) brain homogenates (Frontal Cortex)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Kd</th>
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<tbody>
<tr>
<td>[3H]Abeta reference</td>
<td>10 nM</td>
</tr>
<tr>
<td>[3H]ACI-12589</td>
<td>317 nM</td>
</tr>
</tbody>
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High-resolution ARG\(^2\) on Tau rich AD sections (Entorhinal Cortex)

IHC\(^3\) for Tau (MC1)

ACI-12589 displays selectivity versus co-pathologies such as Abeta and Tau

(1) Alzheimer’s disease; (2) Autoradiography; (3) Immunohistochemistry
ACI-12589: minimal off-target binding

[3H]ACI-12589 assessed for off-target binding to MAO-B<sup>1</sup>

When assessed against 133 receptors and enzymes, only a weak off-target binding was observed for MAO-B confirmed by limited displacement using the MAO-B inhibitor Deprenyl by autoradiography experiments.

<sup>1</sup>Monoamine oxidase-B; (2) Immunohistochemistry
[18F]ACI-12589 as potential first-in-class PET\(^1\) tracer for MSA\(^2\)

Representative PET scan images of MSA and controls

- PET scan images suggest tracer retention in areas affected by disease process in MSA such as the cerebellar white matter and the cerebellar peduncles
- Available clinical data will be presented by Ruben Smith on March 18, 06:45 PM – 07:00 PM, Room Onsite: 114

(1) Positron emission tomography; (2) Multiple system atrophy
[18F]ACI-12589 as potential first-in-class PET\(^1\) tracer for MSA\(^2\)

Data support the further clinical development in MSA, and continuing evaluation in other synucleinopathies

**Preclinical data**

- Significantly improved target binding with clean off-target profile
- Recognition of a-syn\(^3\) inclusions across different synucleinopathies
- Selectivity versus potential co-pathologies
- Pharmacokinetic profile suitable for use as a brain PET imaging agent

**Clinical data**

- Short scan time: good brain uptake and fast signal equilibration
- Substantial tracer retention seen in MSA in expected brain regions
- No clinically relevant in vivo block of cerebellar signal after MAO-B\(^4\) blocking

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(1) Positron emission tomography; (2) Multiple system atrophy; (3) Alpha-synuclein; (4) Monoamine oxidase-B
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