Novel PET Tracers of α-Synuclein for the Diagnosis of Parkinson’s Disease
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Disclosures

Andreas Muhs is a full employee of AC Immune
No off-label nor investigational use of therapeutic products will be presented
AC Immune’s proprietary chemical library

The Morphomer™ platform

- Originated from patent application WO2005081897A2 by Jean-Marie Lehn and colleagues describing “compositions comprising non-peptide small molecules that solubilize beta-amyloid peptide fiber”

- Compounds designed to selectively bind protein aggregates

- Compound classes are CNS-directed

- Morphomer™ is a general term to describe small molecules designed at AC Immune
Clinical need for an αSynuclein radiotracer

Biomarker for early diagnosis and disease progression

- >90% of PD cases are sporadic: Diagnoses can not rely on genetic testing\(^{(1)}\)
- Dopaminergic imaging criticized for poor correlation with clinical outcomes\(^{(2,3)}\)
- αSynuclein inclusions (Lewy bodies) appear before dopaminergic changes, i.e., premotor PD\(^{(4)}\)
- Imaging αSynuclein could better predict premotor PD\(^{(5)}\)
- Potentially useful as surrogate marker in clinical trials

\(1\) Shat et al., 2016 Journal of Nuclear Medicine
\(3\) Brooks et al., 2003 Exp Neurol.
\(4\) Hawkes et al., 2010 Parkinsonism Relat Disord.
\(5\) Dickson et al., 2009 Lancet Neurol.
αSynuclein radiotracer

Specific challenges for PET ligand development

- Pathological αSynuclein detected in multiple forms: Lewy bodies, fibrils, oligomers and pore-like species\(^1\)
- αSynuclein deposits contain other proteins: parkin, tau, amyloid beta, etc\(^2\)
- Pathological αSynuclein can be extensively modified post-translationally\(^3, 4\)
- Pathological aggregates of αSynuclein are not as abundant as amyloid beta, thus high selectivity for αSynuclein over amyloid beta and tau is required\(^5\)

\(^{1}\) Paleologou et al., 2009 Brain
\(^{2}\) Kotzbauer et al., 2012 Arch Neurol.
\(^{3}\) Schildknecht et al., 2013 J Neurochem.
\(^{4}\) Anderson et al., 2006 J Biol Chem.
\(^{5}\) Eberling et al., 2013 J Parkinsons Dis
Affinity measurements on αSynuclein Fibrils

Radio-binding using 3H-Cpd-G’

<table>
<thead>
<tr>
<th>[3H]-Cpd-G’</th>
<th>Ki (nM)</th>
<th>95% Confidence Intervals</th>
</tr>
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<tbody>
<tr>
<td>Cpd-G’</td>
<td>9.2</td>
<td>3.9 to 21.4</td>
</tr>
<tr>
<td>Cpd-H’</td>
<td>5.8</td>
<td>1 to 32.8</td>
</tr>
<tr>
<td>Cpd-F’</td>
<td>2.0</td>
<td>0.5 to 7.3</td>
</tr>
</tbody>
</table>

Cpd-F’ and Cpd-H’ both show low nM binding affinity to αSynuclein fibrils

Ref.: AC Immune unpublished data
Target engagement on Braak stage V-VI PD tissue

Representative results of staining amygdala tissue sections

Both compounds show good staining of αSynuclein aggregates. Staining of αSynuclein aggregates is maintained at 500 nM of Cpd-F’.
Target engagement on early PD Braak stage III-IV

Representative results of staining amygdala tissue sections

Despite lower abundance of αSynuclein aggregates, both compounds show target engagement
Target engagement on Dementia with Lewy Bodies
Representative results of staining cingulate cortex tissue sections

Both compounds show staining of αSynuclein aggregates present in DLB
Target engagement on Multiple System Atrophy – Type C

Representative results of staining pons tissue sections

Staining with both compounds colocalize with αSynuclein immunostaining of glial cytoplasmic inclusions

Ref.: AC Immune unpublished data
Selectivity over beta-Amyloid in Alzheimer’s Disease

Representative results of staining amygdala tissue sections

Cpd-F’ and Cpd-H’ (not shown) do not stain Amyloid beta plaques

Ref.: AC Immune unpublished data
Selectivity over beta-Amyloid in Parkinson’s Disease
Representative results of staining amygdala tissue sections

Cpd-F’ selectively stains αSynuclein aggregates decorating Amyloid beta plaques in PD tissue with mixed pathology

Representative results of staining amygdala tissue sections, scale bar: 50 µm
Selectivity over beta-Amyloid in Alzheimer’s Disease

Autoradiography on amygdala tissue with a beta-Amyloid ligand

Both compounds do not compete a beta-amyloid ligand on AD amygdala sections
Pharmacokinetics
Cold i.v. PK assessment at 1mg/kg in mouse

Cpd-H’ shows promising PK profile with good uptake and fast washout.
Cpd-F’ shows low brain uptake but fast washout.

Ref.: AC Immune unpublished data
PET radioligands for αSynuclein

Conclusions

- αSynuclein is an excellent target for PET radiotracer development for Parkinson’s disease and for other synucleinopathies

- Cpd-F’ and Cpd-H’ have been identified as lead compounds and they show:
  - Low nM affinity to αSynuclein fibers
  - Target engagement on αSynuclein aggregates from different synucleinopathies
  - Selectivity over amyloid beta

- Cpd-H’ has a pharmacokinetic profile that can allow its use as PET tracer
Thank you!

AC Immune team

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Elpida Tsika
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Luigino Grasso
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Biogen team

Shailendra Patel
Liz Norton
Ashley Knight
Nancy Stratman
Sara Girmay
Ajay Purohit
David Paterson

Acknowledgements