JPND research

EU Joint Programme – Neurodegenerative Disease Research

# OligoFIT

## [Oligomer-Focused Screening and Individualized Therapeutics to target Neurodegenerative Disorders]


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DEVELOPING INNOVATIVE VACCINES

NUFFIELD DEPARTMENT of MEDICINE

UNIVERSITY OF OXFORD

# OligoFIT Partners [all thanks to these people]

Latvian Biomedical Research and Study Centre
research and education in biomedicine from genes to human

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**United Kingdom**

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***Coordinator***

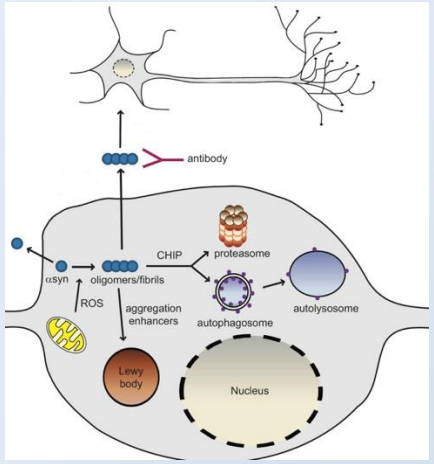
# Goals [what are we trying to achieve?]

One protein – multiple diseases / clinical manifestations ?

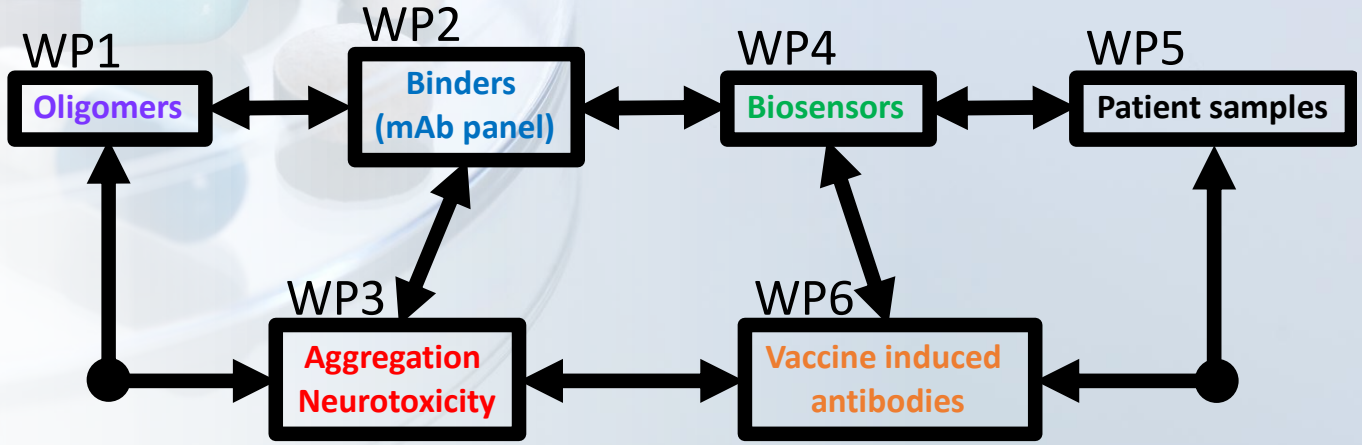
Better appreciation of the complexities of small aggregate species (oligomers)

Understanding aggregation behaviour and early detection

Rationale for selected targeting of distinct ‘toxic’ forms as therapeutic interventions (?)




Tran *et al.*, (2014) *Cell Reports*

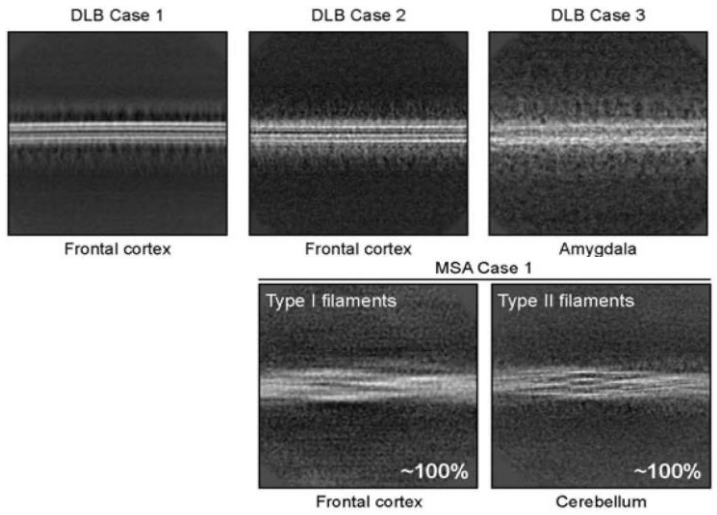


# Oligomers: different strains ?

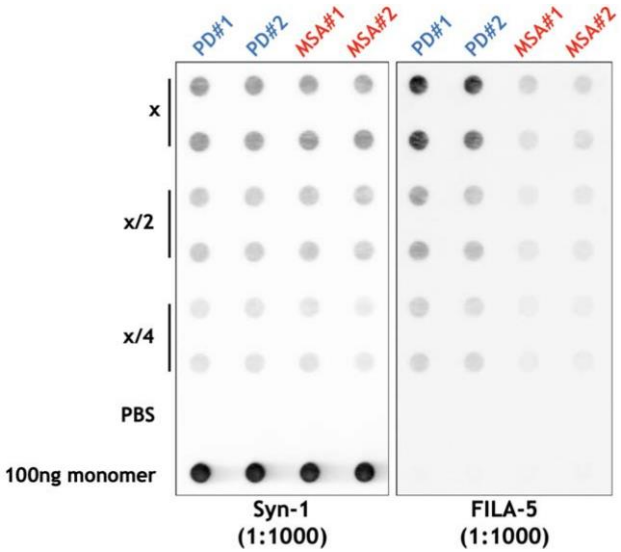
In 2020, groups isolated aggregated fibrils from patient samples exhibiting different shapes.

This supports that potential strains exist

**Shapes of each strain can act as seeds for further templated aggregation**




Can antibodies discriminate **PD** from **MSA** ?




Unpublished H. Lundbeck A/S & Jensen labs


Shahnawaz M, *et al.*, Discriminating α-synuclein strains in Parkinson's disease and multiple system atrophy. Nature. 2020 Feb;578(7794):273-277.

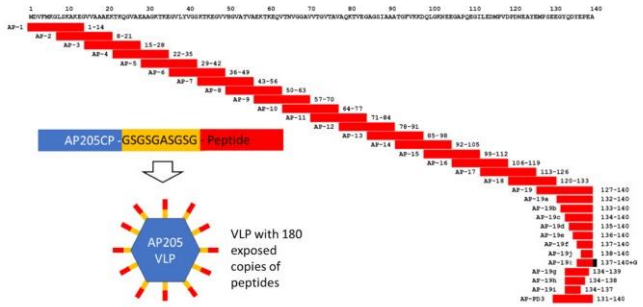
Schweighauser M, *et al.*, Structures of α-synuclein filaments from multiple system atrophy. Nature. 2020 Sep;585(7825):464-469.

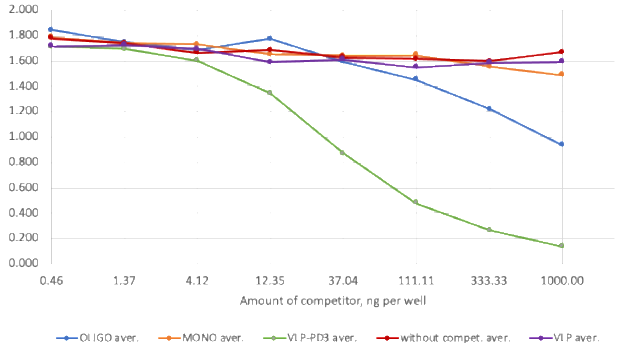
# Selected Highlights [1]

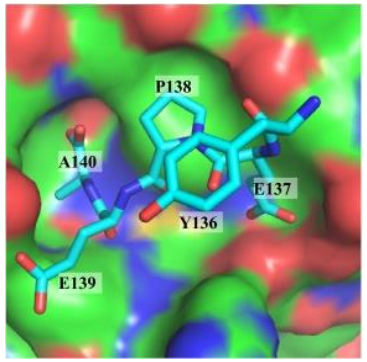
VLP = virus-like particle
Self-assembling from single viral coat protein

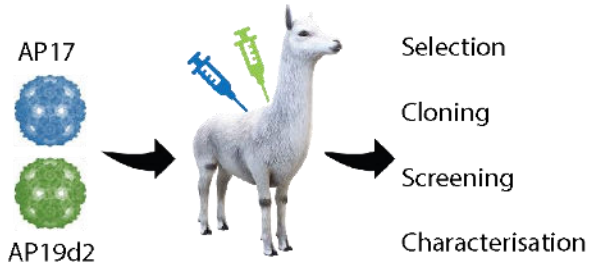
- VLP-based oligomer mimetics to probe aggregate specific antibodies
  - MJFR-14-6-4-2 commercially available aggregate specific mAb
- **VLP-construct out competes oligomers**
- Better way to probe Ab and to generate new Ab's

(panel of nanobodies generated – characterisation ongoing)



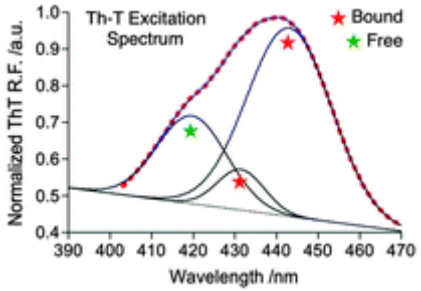



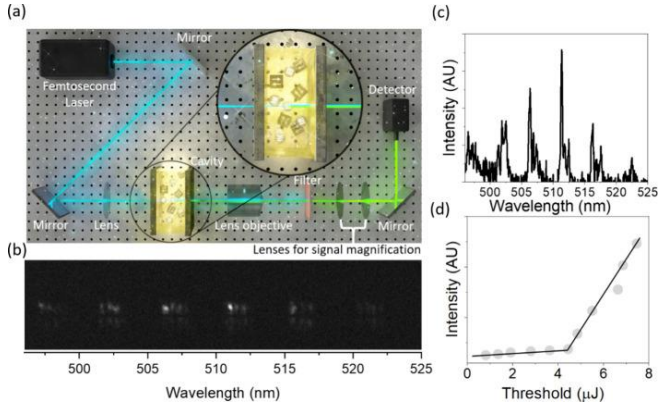

Liekniņa I, Reimer L, Panteļejevs T, Lends A, Jaudzems K, El-Turabi A, Gram H, Hammi A, Jensen PH, Tārs K. **Structural basis of epitope recognition by anti-alpha-synuclein antibodies MJFR14-6-4-2.** NPJ Parkinsons Dis. 2024 Oct 27;10(1):206. doi: 10.1038/s41531-024-00822-y.

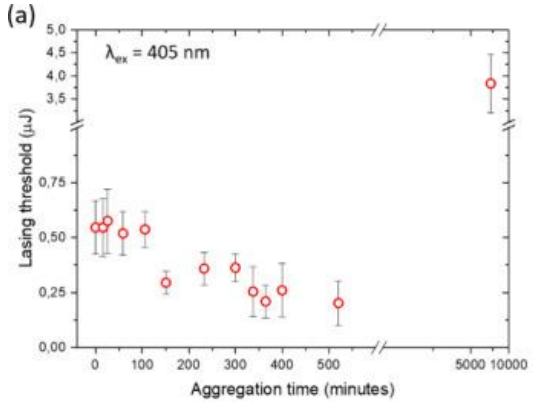
# Selected Highlights [2]

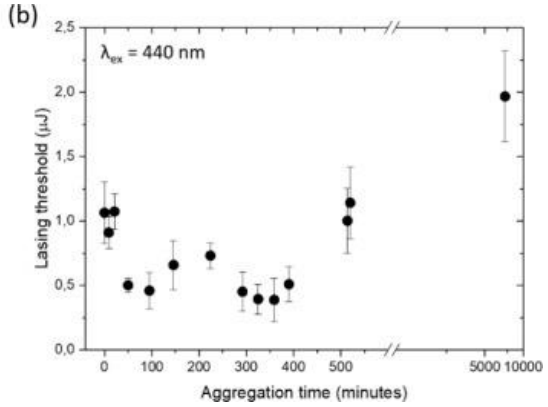
- Biophysical analyses of aggregation characteristics, oligomer heterogeneity and co-aggregation
  - *LASER-based measurements of ThT fluorescence reveal differences between bound and free states*

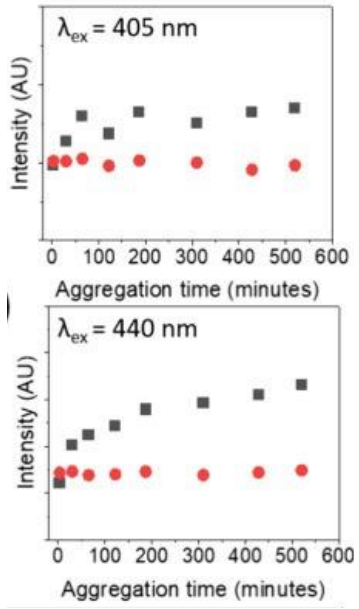



- ThT binding can be detected by an increase in microviscosity
  - *Lasing threshold at distinct wavelengths reveals differences in early aggregation events (before fibrillisation)*



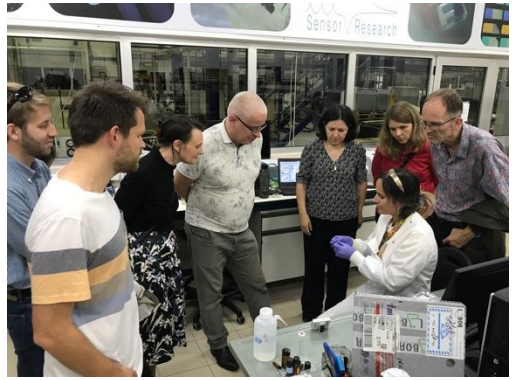



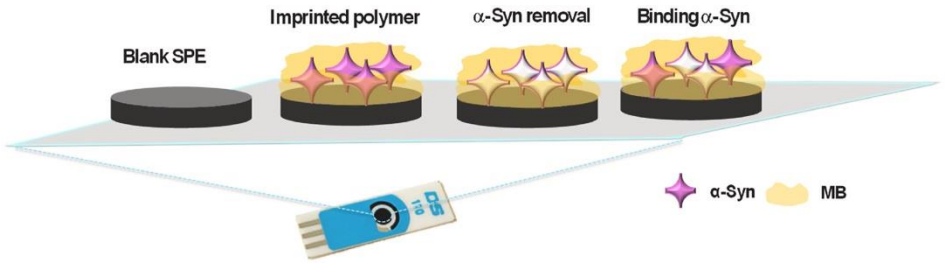

Steady State vs Time-resolved fluorescence views of early aggregation

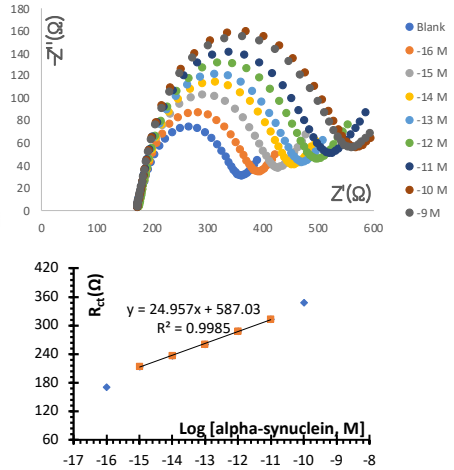
Rusakov K, El-Turabi A, Reimer L, Jensen PH, Hanczyc P. **Thioflavin T–a Reporter of Microviscosity in Protein Aggregation Process: The Study Case of α-Synuclein.** J Phys Chem Lett. 2024 Jun 27;15(25):6685-6690. doi: 10.1021/acs.jpclett.4c00699.

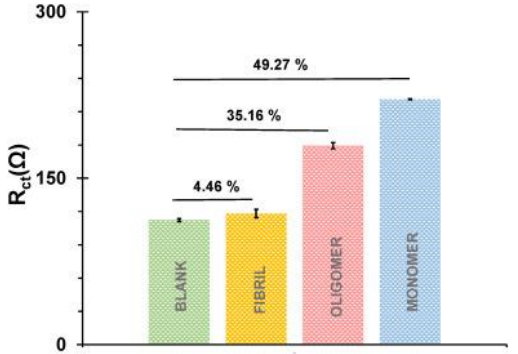
# Selected Highlights [3]

- Site visit to Coimbra to learn about novel biosensor research and exchange ideas for prototype designs
  - Plastic antibodies sensor shows high sensitivity for α-syn (fM – aM range)
  - Not responsive with fibrillar aggregate species
- Studies with prototype immune-based sensors using aggregate specific mAb's ongoing





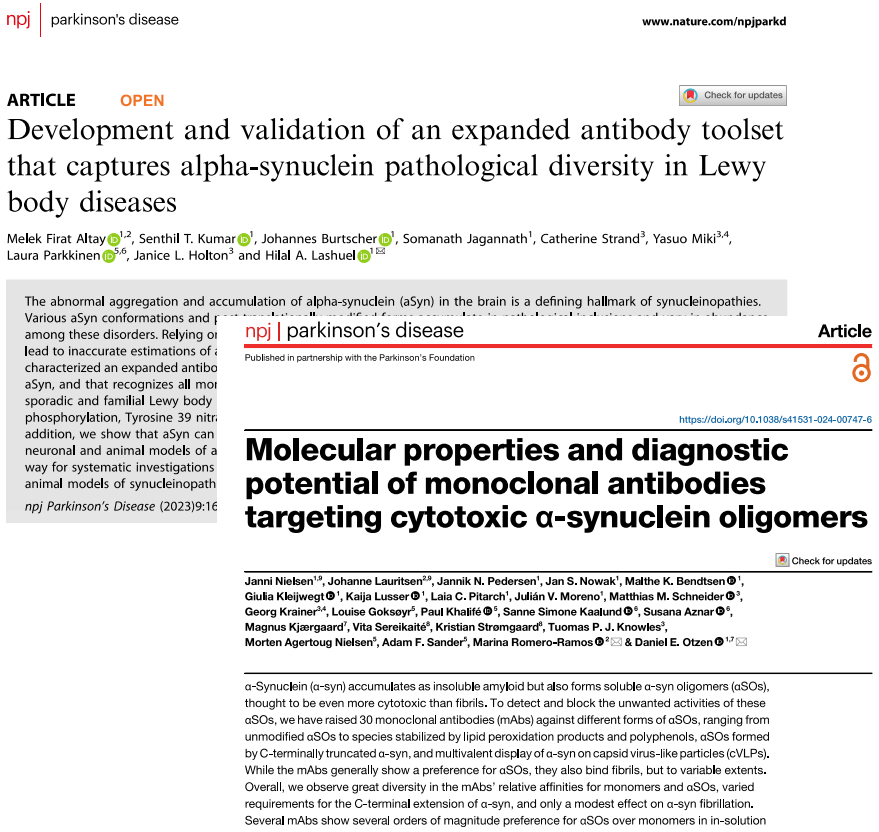

Molecular imprinted biosensor displays high sensitivity for α-syn in CSF samples

da Silva IS, Cardoso AR, Reimer L, König A, van Riesen C, Outeiro TF, Jensen PH, Sales MGF. **α-Synuclein plastic antibody applied to monitor monomeric structures and discriminate aggregated forms in human CSF.** Biosens Bioelectron. 2025 Jan 15;268:116880. doi: 10.1016/j.bios.2024.116880.

# Why better antibodies still matter

Greater appreciation of complexities of aggregated intermediates translate to better targeted therapies

## Improve species definitions for basic research



npj | parkinson's disease

www.nature.com/npjparkd

ARTICLE OPEN

Check for updates

Development and validation of an expanded antibody toolset that captures alpha-synuclein pathological diversity in Lewy body diseases

Melek Firat Altay[1,2], Senthil T. Kumar[1], Johannes Burtscher[1], Somanath Jagannath[1], Catherine Strand[3], Yasuo Miki[3,4], Laura Parkkinen[5,6], Janice L. Holton[3] and Hilal A. Lashuel[1]✉

The abnormal aggregation and accumulation of alpha-synuclein (aSyn) in the brain is a defining hallmark of synucleinopathies. Various aSyn conformations and p… among these disorders. Relying o… lead to inaccurate estimations of … characterized an expanded antibo… aSyn, and that recognizes all mo… sporadic and familial Lewy body … phosphorylation, Tyrosine 39 nitr… addition, we show that aSyn can … neuronal and animal models of a… way for systematic investigations … animal models of synucleinopath…

npj Parkinson's Disease (2023)9:16

npj | parkinson's disease

Article

Published in partnership with the Parkinson's Foundation

https://doi.org/10.1038/s41531-024-00747-6

Molecular properties and diagnostic potential of monoclonal antibodies targeting cytotoxic α-synuclein oligomers

Check for updates

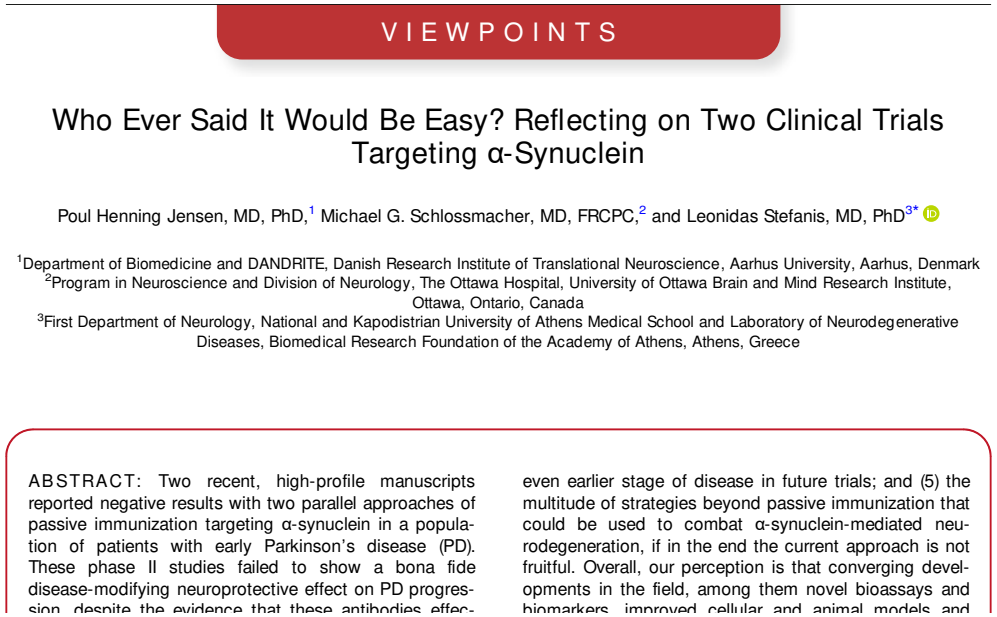
Janni Nielsen[1,9], Johanne Lauritsen[2,9], Jannik N. Pedersen[1], Jan S. Nowak[1], Malthe K. Bendtsen[1], Giulia Kleijwegt[1], Kaija Lusser[1], Laia C. Pitarch[1], Julián V. Moreno[1], Matthias M. Schneider[3], Georg Krainer[3,4], Louise Goksøyr[2], Paul Khalifé[5], Sanne Simone Kaalund[6], Susana Aznar[6], Magnus Kjærgaard[7], Vita Sereikaitė[8], Kristian Strømgaard[8], Tuomas P. J. Knowles[3], Morten Agertoug Nielsen[5], Adam F. Sander[2], Marina Romero-Ramos[2]✉ & Daniel E. Otzen[1,7]✉

α-Synuclein (α-syn) accumulates as insoluble amyloid but also forms soluble α-syn oligomers (αSOs), thought to be even more cytotoxic than fibrils. To detect and block the unwanted activities of these αSOs, we have raised 30 monoclonal antibodies (mAbs) against different forms of αSOs, ranging from unmodified αSOs to species stabilized by lipid peroxidation products and polyphenols, αSOs formed by C-terminally truncated α-syn, and multivalent display of α-syn on capsid virus-like particles (cVLPs). While the mAbs generally show a preference for αSOs, they also bind fibrils, but to variable extents. Overall, we observe great diversity in the mAbs' relative affinities for monomers and αSOs, varied requirements for the C-terminal extension of α-syn, and only a modest effect on α-syn fibrillation. Several mAbs show several orders of magnitude preference for αSOs over monomers in in-solution

doi:10.1038/s41531-023-00604-y

doi:10.1038/s41531-024-00747-6

## Improve candidates going to clinical trials



VIEWPOINTS

Who Ever Said It Would Be Easy? Reflecting on Two Clinical Trials Targeting α-Synuclein

Poul Henning Jensen, MD, PhD,[1] Michael G. Schlossmacher, MD, FRCPC,[2] and Leonidas Stefanis, MD, PhD[3*]

[1]Department of Biomedicine and DANDRITE, Danish Research Institute of Translational Neuroscience, Aarhus University, Aarhus, Denmark
[2]Program in Neuroscience and Division of Neurology, The Ottawa Hospital, University of Ottawa Brain and Mind Research Institute, Ottawa, Ontario, Canada
[3]First Department of Neurology, National and Kapodistrian University of Athens Medical School and Laboratory of Neurodegenerative Diseases, Biomedical Research Foundation of the Academy of Athens, Athens, Greece

ABSTRACT: Two recent, high-profile manuscripts reported negative results with two parallel approaches of passive immunization targeting α-synuclein in a population of patients with early Parkinson's disease (PD). These phase II studies failed to show a bona fide disease-modifying neuroprotective effect on PD progression, despite the evidence that these antibodies effec… even earlier stage of disease in future trials; and (5) the multitude of strategies beyond passive immunization that could be used to combat α-synuclein-mediated neurodegeneration, if in the end the current approach is not fruitful. Overall, our perception is that converging developments in the field, among them novel bioassays and biomarkers, improved cellular and animal models and…

Jensen PH, Schlossmacher MG, Stefanis L. **Who Ever Said It Would Be Easy? Reflecting on Two Clinical Trials Targeting α-Synuclein.** Mov Disord. 2023 Mar;38(3):378-384. doi: 10.1002/mds.29318.

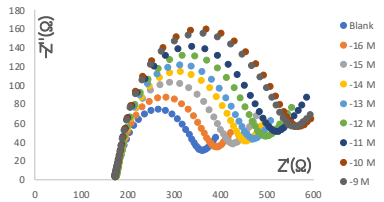
# Summary

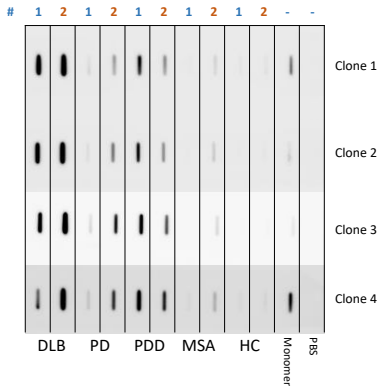
**Harmonisation of reagents essential**

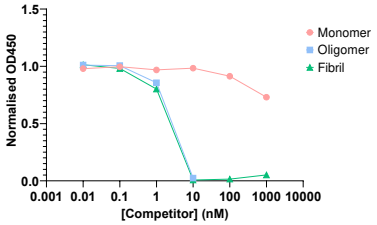
**Shapes (conformers) can be discriminated**

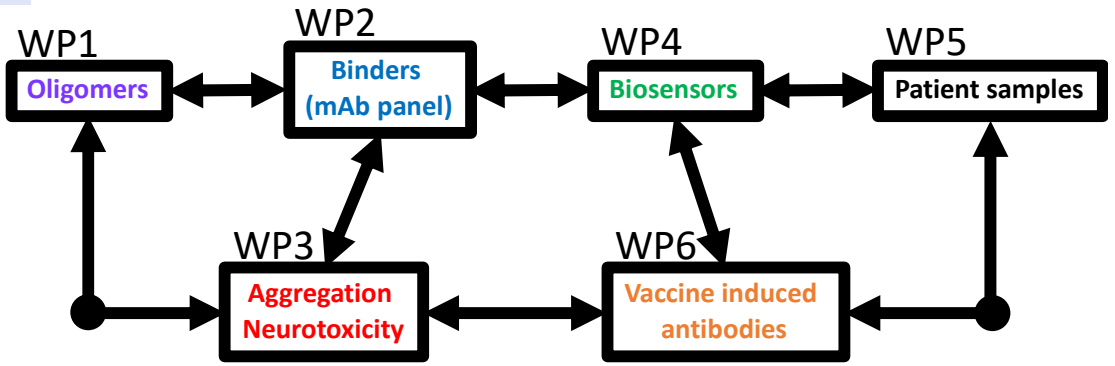
**New techniques and tools developed**

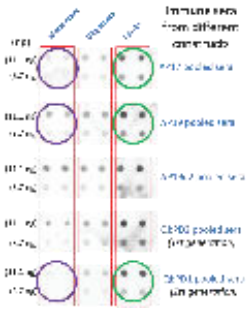
**Inclusivity matters: all can contribute**

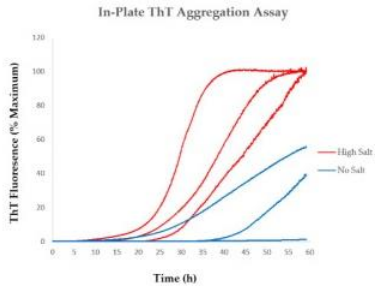


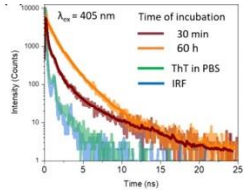



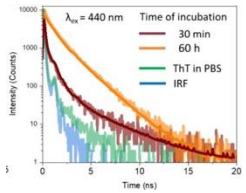



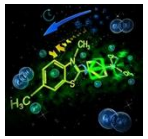



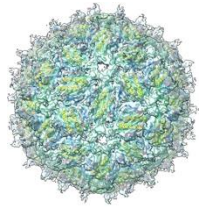



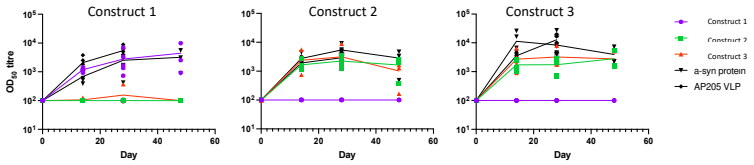






# Benefits/ Outcomes [Thank you ]

- Scientific papers/ presentations
  - Peer-reviewed (8), book chapters (2) and conference posters (4)
  - Support for conference attendance of junior members
  - International collaborations

- Next steps
  - Frontier Grant programme from Lundbeck Foundation (Lasse Reimer awarded DKK 5 million)
  - Other members secured their next post and/or completed their studies (Doctorate and Masters)

- Interactions with patients and carers
  - Met people with lived experiences of disease
  - Listened and answered questions and comments on our research
  - Idea: a series of lay explanations/ commentary for the community