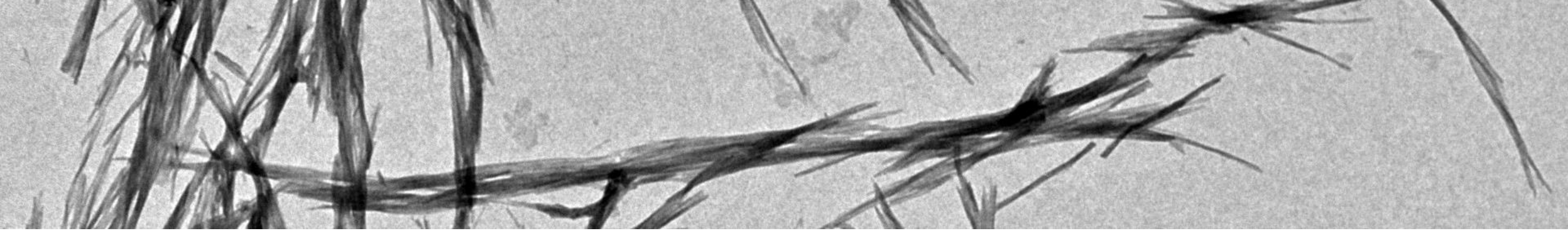


Protein Folding and Conformational Diseases Lab

SALVADOR VENTURA

Institute of Biotechnology and Biomedicine & Dept. Biochemistry and Molecular Biology – UAB

Institute of Research and Innovation Parc Taulí (I3PT-CERCA)

The Approach

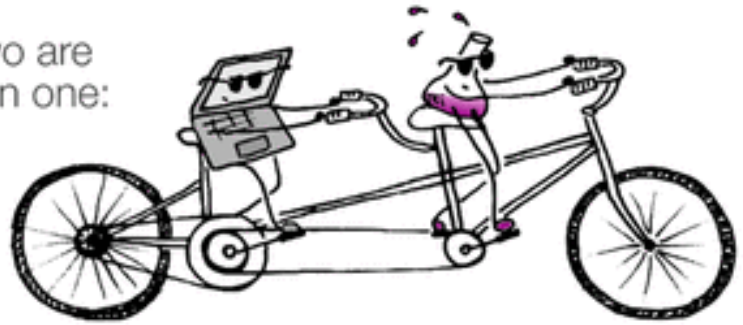
Our laboratory employs **a multidisciplinary** and collaborative approach to studying **protein folding, misfolding, and aggregation**. Our primary **objective is to develop novel therapeutics and diagnostic tools to target these pathologies effectively**.

Design and **manufacture advanced protein-based biopharmaceuticals.** Additionally, we are committed to exploring **the potential of self-assembled functional materials for nanotechnology and biomedical applications**.

EXAMPLE I: Computation

Computation

When two are better than one:



Computation & Experiment in Synergy

2007

Aggrescan
Prediction of "hot spots" of aggregation in polypeptides.

2014

PrionScan
An online database of predicted prion domains in complete proteomes

PrionW
Identification of prion-like protein domains

2015

A3D
A server for prediction of aggregation propensity in protein structures and rational design of protein solubility.

AMYCO
A server for prediction of the impact of mutations on the aggregation propensity of prion-like proteins

2019

A3D 2.0
Major update from A3D including stability measures, automatic redesign of solubility, increased computational resources for protein complexes, REST-ful mode and a standalone version.

SolupHred
A Server to Predict the pH-dependent Aggregation of Intrinsically Disordered Proteins

2020

DispHred
A Server to Predict pH-Dependent Order–Disorder Transitions in Intrinsically Disordered Proteins

DispHScan
A Multi-Sequence Web Tool for Predicting Protein Disorder as a Function of pH

2021

SGnn
A server for the prediction of prion-like domains recruitment to stress granules upon heat stress

CARs-DB
A database of Cryptic Amyloidogenic Regions in Intrinsically Disordered Proteins

2022

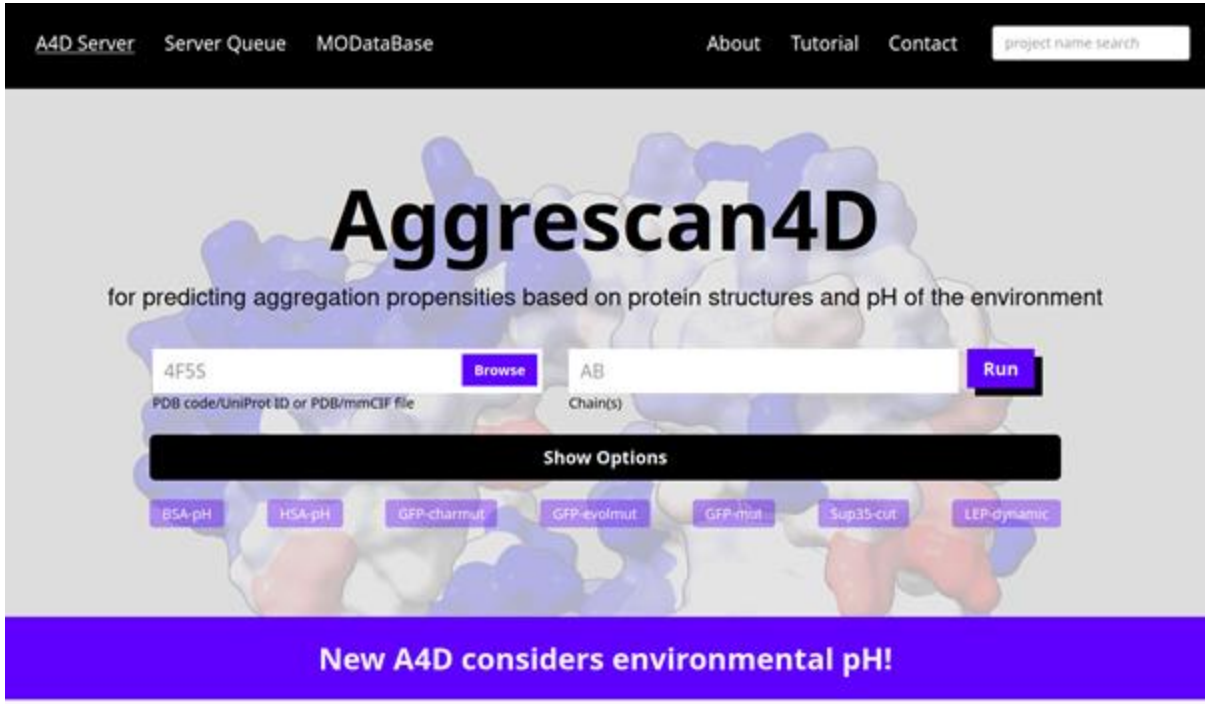
A3D Database
Structure-based predictions of protein aggregation for the human proteome

The environment: Aggrescan4D

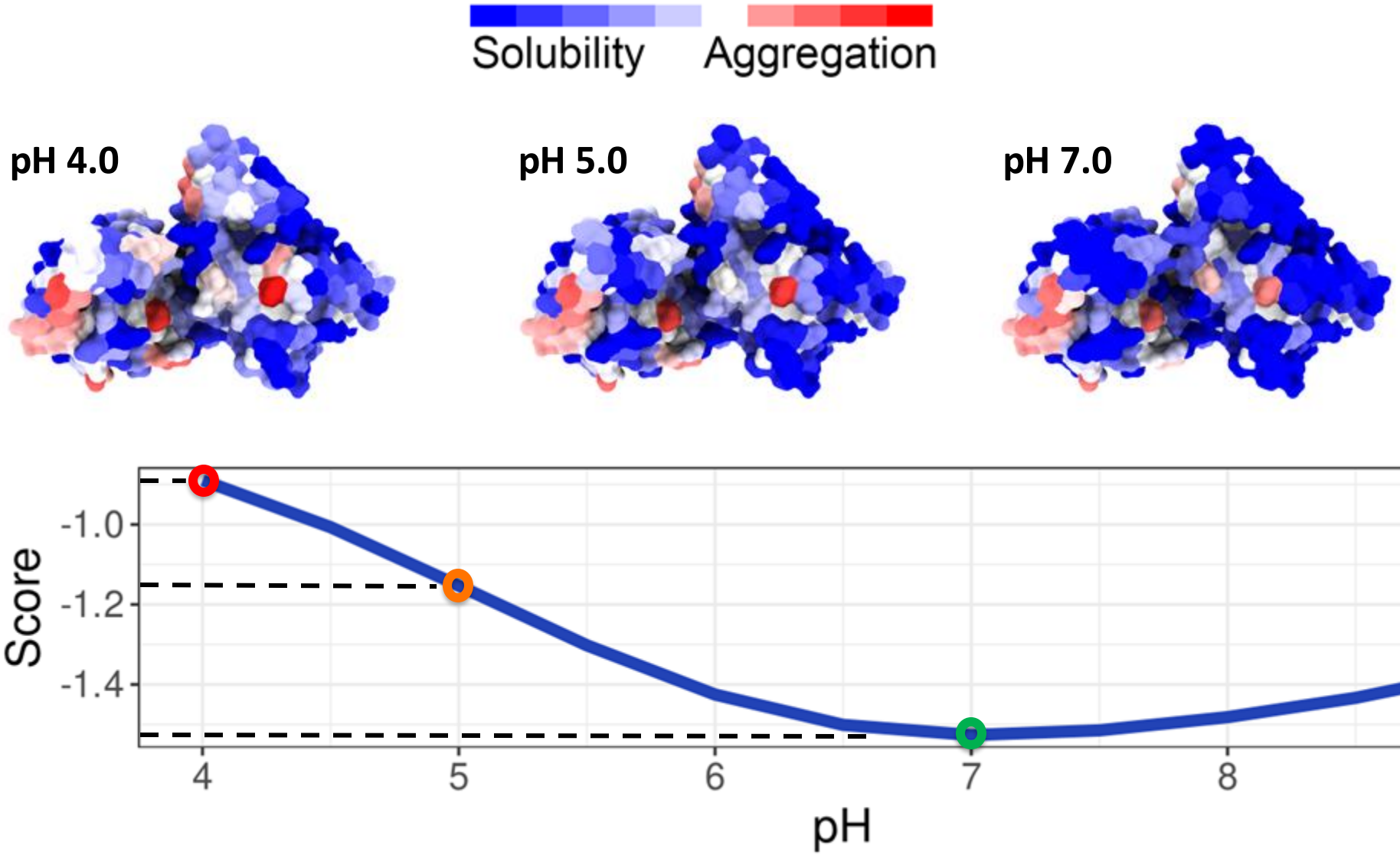
Nucleic Acids Research

Aggrescan4D: structure-informed analysis of pH-dependent protein aggregation

Oriol Bárcenas [1], Aleksander Kuriata [2], Mateusz Zalewski [2], Valentín Iglesias [1,3], Carlos Pintado-Grima [1], Grzegorz Firlik [2], Michał Burdukiewicz [1,3], Sebastian Kmiecik [2,*] and Salvador Ventura [1,*]

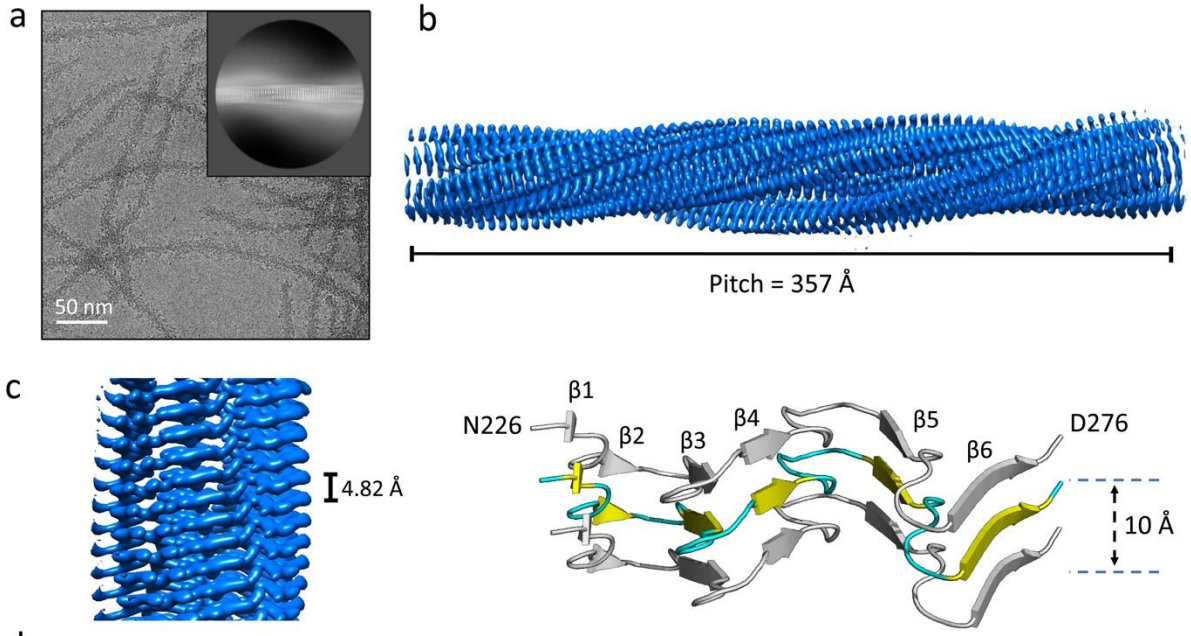


pH-dependent aggregation prediction



EXAMPLE II:
Amyloid structure

Cryo-EM structure determination of hnRNPDL-2 amyloid fibrils

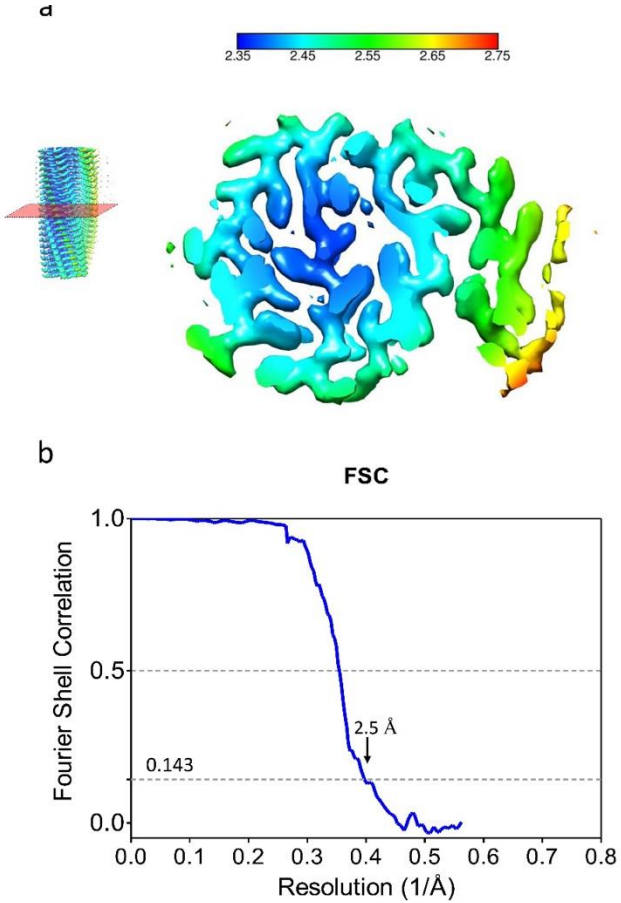


nature communications

Article

https://doi.org/10.1038/s41467-023-35854-0

Cryo-EM structure of hnRNPDL-2 fibrils, a functional amyloid associated with limb-girdle muscular dystrophy D3



EXAMPLE III:
Building up BioNanomaterials

MPPs form fibrillar amyloid assemblies

PrionW: a server to identify proteins containing glutamine/asparagine rich prion-like domains and their amyloid cores

Rafael Zambrano[1,†], Oscar Conchillo-Sole[1,†], Valentin Iglesias[1,†], Ricard Illa[1], Frederic Rousseau[2], Joost Schymkowitz[2], Raimon Sabate[3], Xavier Daura[1,4] and Salvador Ventura[1,*]

Nucleic Acids Research

ACS NANO

Cite This: *ACS Nano* 2018, 12, 5394–5407

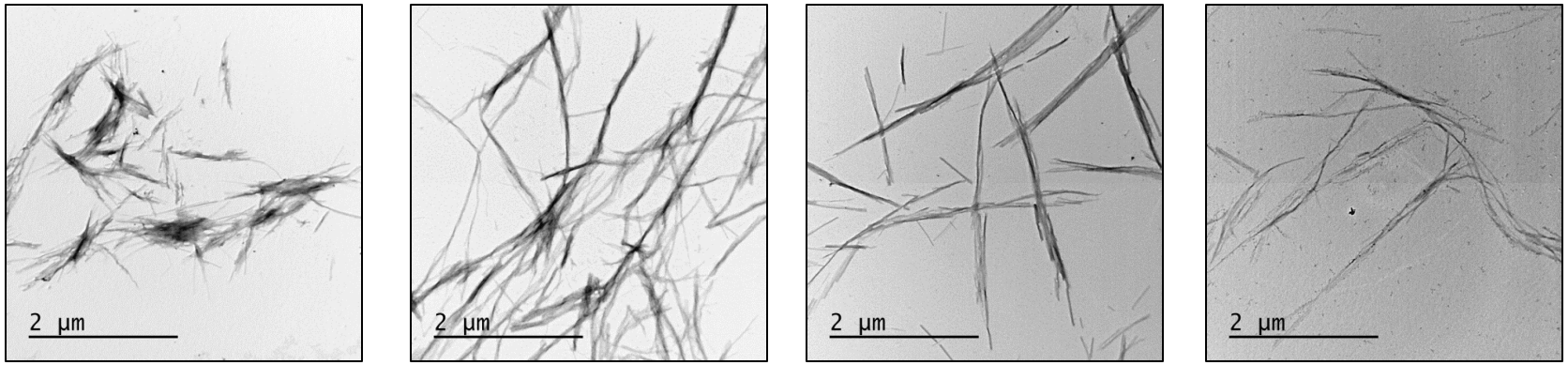
www.acsnano.org

ARTICLE

Minimalist Prion-Inspired Polar Self-Assembling Peptides

Marta Díaz-Caballero,[†] Susanna Navarro,[†] Isabel Fuentes,[‡] Francesc Teixidor,[‡] and Salvador Ventura[*,†]

NY7 QY7 SY7 GY7



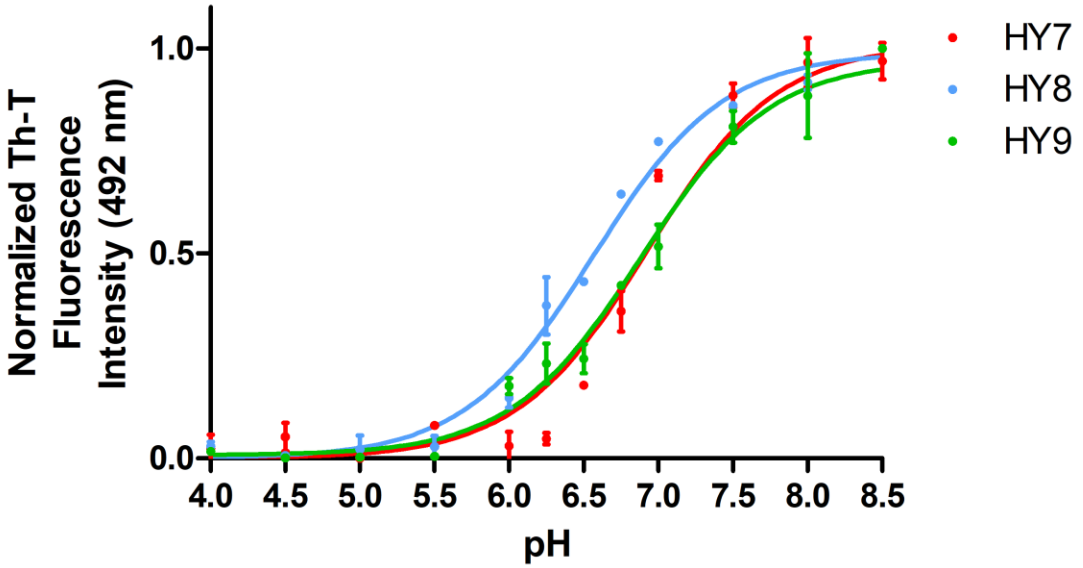
Amyloid self-assembly of HY-peptides is controlled by pH

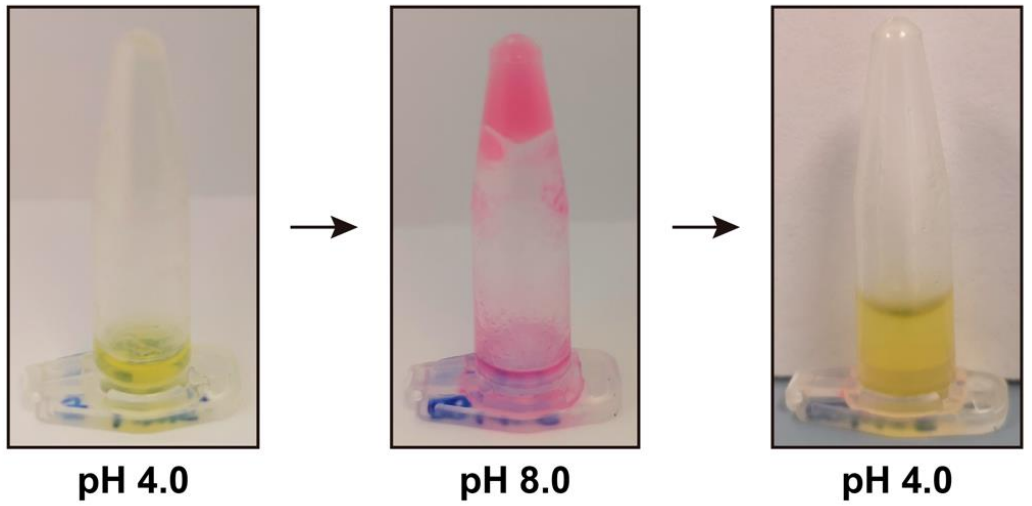
ACS Catalysis

pubs.acs.org/acscatalysis Research Article

pH-Responsive Self-Assembly of Amyloid Fibrils for Dual Hydrolase-Oxidase Reactions

Marta Díaz-Caballero, Susanna Navarro, Miquel Nuez-Martínez, Francesca Peccati, Luis Rodríguez-Santiago, Mariona Sodupe, Francesc Teixidor, and Salvador Ventura*





Metallized MPPs behave as ancestral enzymes: Carbonic anhydrase activity

ACS NANO

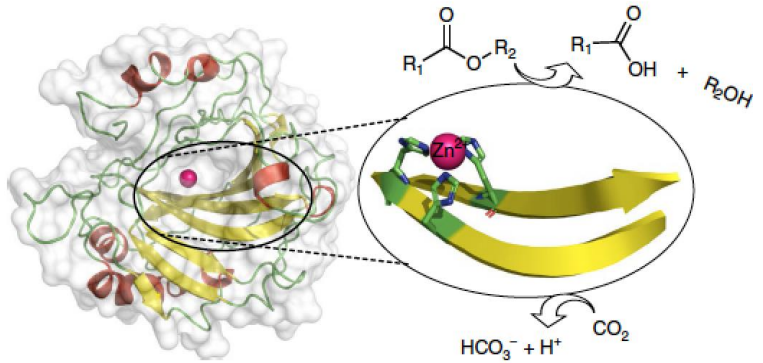
www.acsnano.org

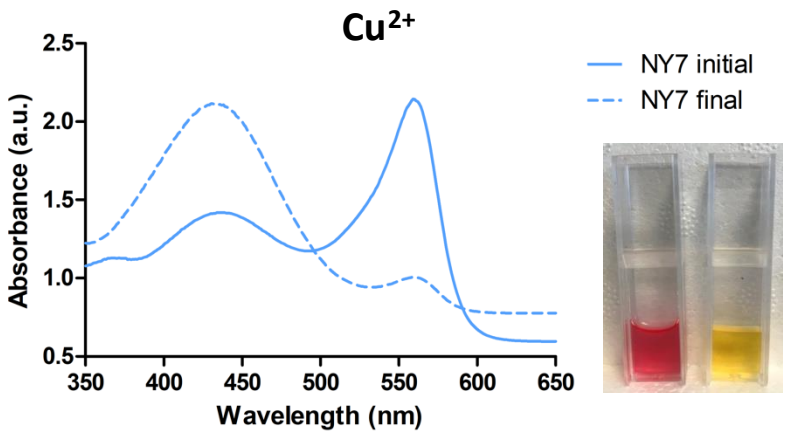
ARTICLE

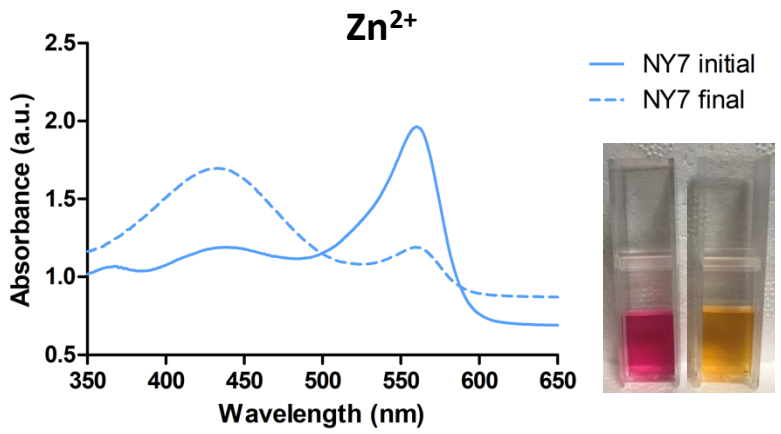
Amyloid Fibrils Formed by Short Prion-Inspired Peptides Are Metalloenzymes

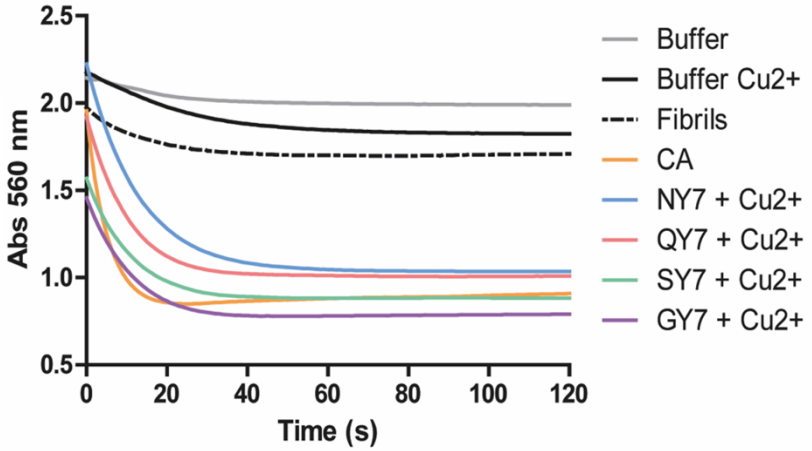
Susanna Navarro, Marta Díaz-Caballero, Francesca Peccati, Lorena Roldán-Martín, Mariona Sodupe, and Salvador Ventura*

Human carbonic anhydrase









Metallized MPPs behave as carbonic anhydrase-active scaffolds

Díaz-Caballero *et al.*, ACS Nano 2023

Bridging Cells

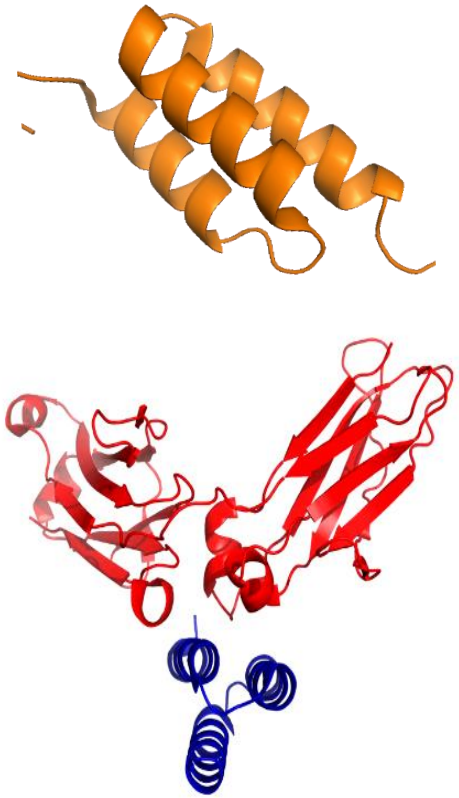
ACS APPLIED MATERIALS & INTERFACES

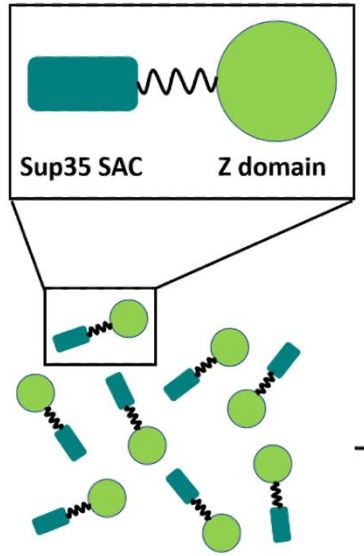
www.acsami.org Research Article

Dual Antibody-Conjugated Amyloid Nanorods to Promote Selective Cell–Cell Interactions

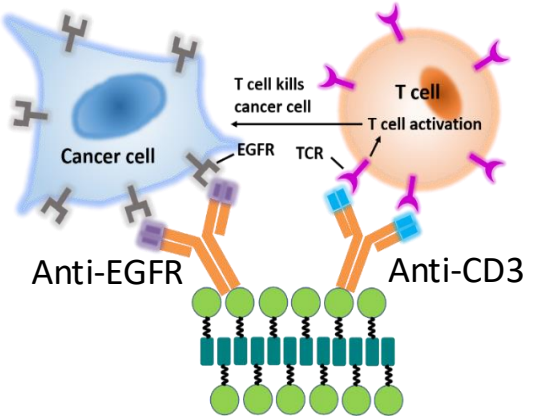
Weiqiang Wang, Marcos Gil-Garcia, and Salvador Ventura*

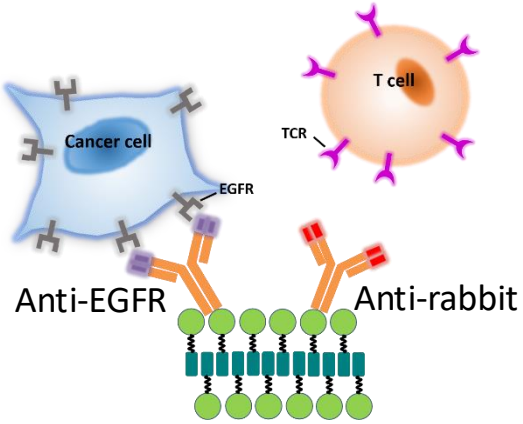
Z-domain

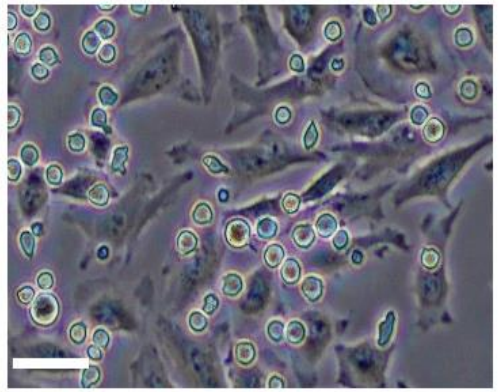


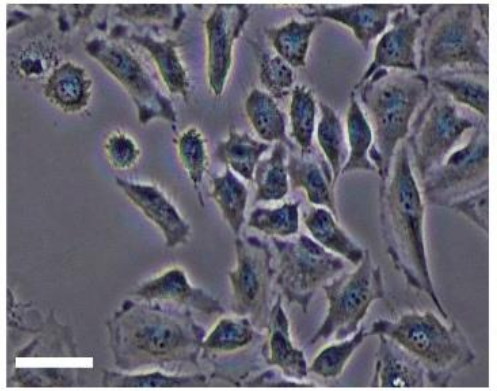


Self-assembly

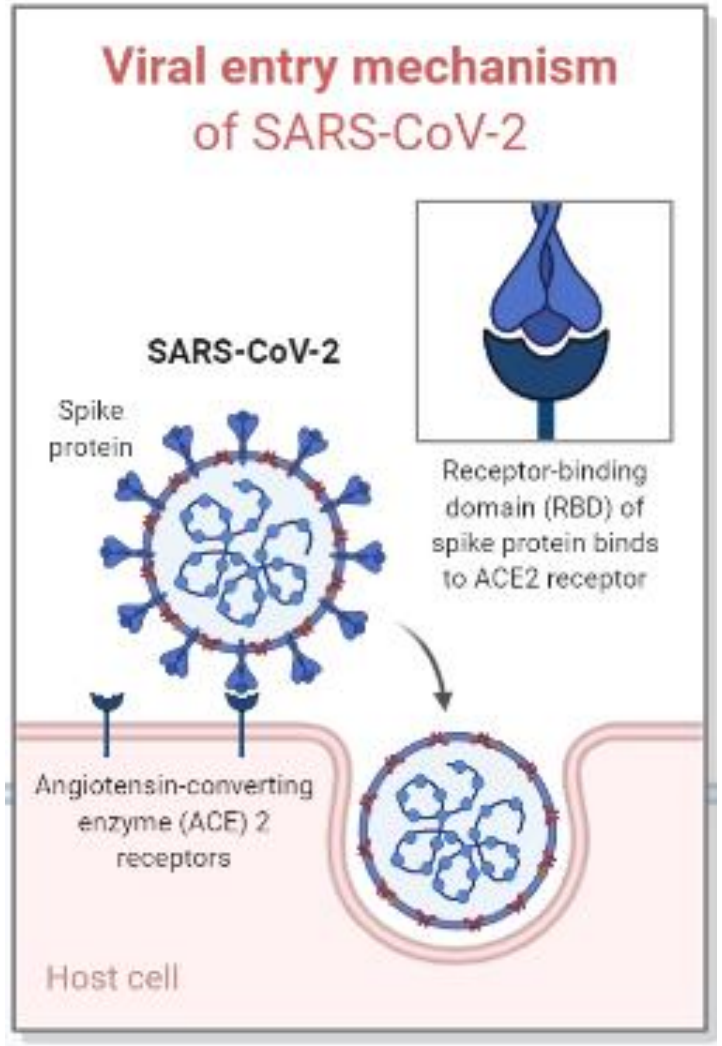








Capture Viruses



Journal of Colloid and Interface Science 674 (2024) 753–765

Contents lists available at ScienceDirect

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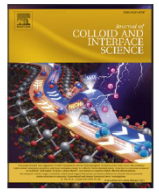
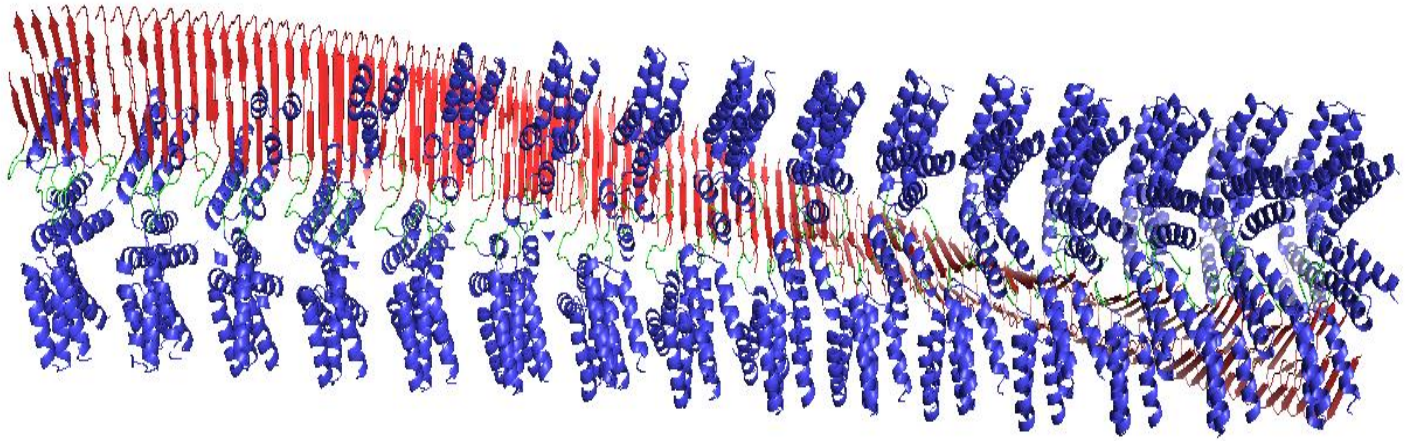
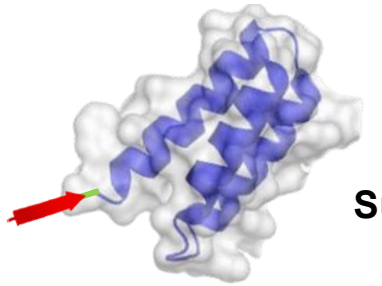
journal homepage: www.elsevier.com/locate/jcis



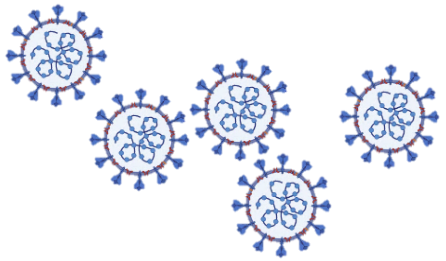
Bioengineered self-assembled nanofibrils for high-affinity SARS-CoV-2 capture and neutralization

Molood Behbahanipour, Susanna Navarro, Oriol Bárcenas, Javier Garcia-Pardo, Salvador Ventura *





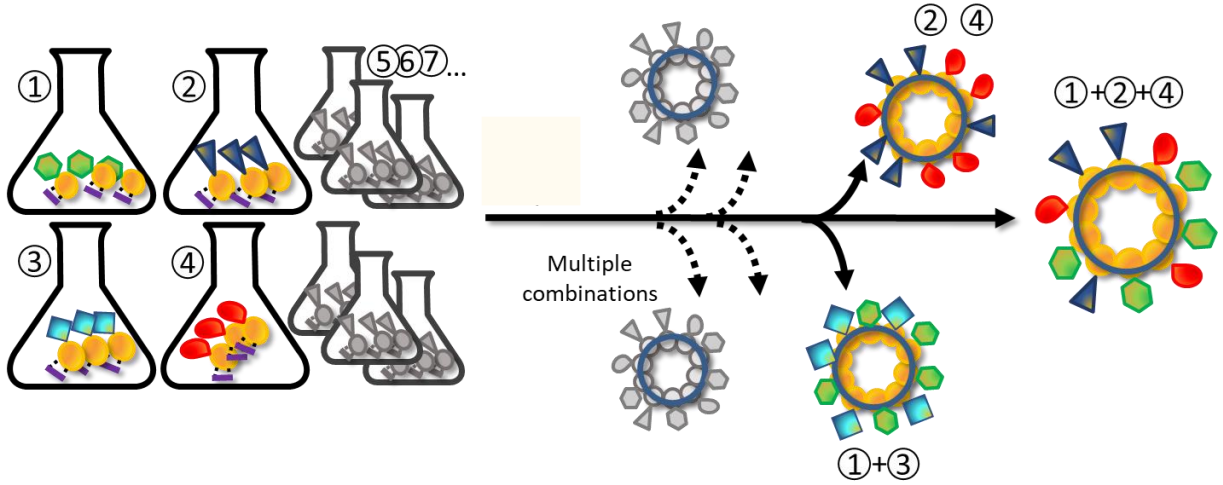
Sup35-LCB1



Ring Technology

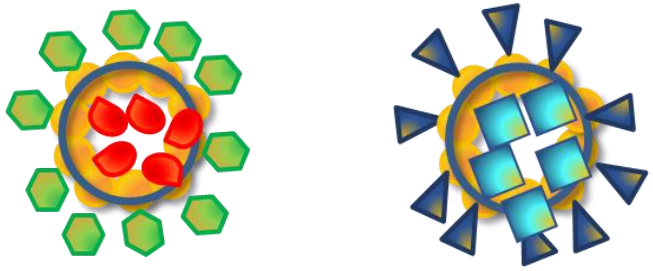
Through rational protein design and engineering, we have modified the self-assembling properties of viral proteins and generated a minimal toolkit for on-demand oligomerization

Controlled self-assembly in a Lego-like fashion
RLP-S1, RLP-S2 & RLP-S3



On-demand self assembly of heterooligomeric RLPs

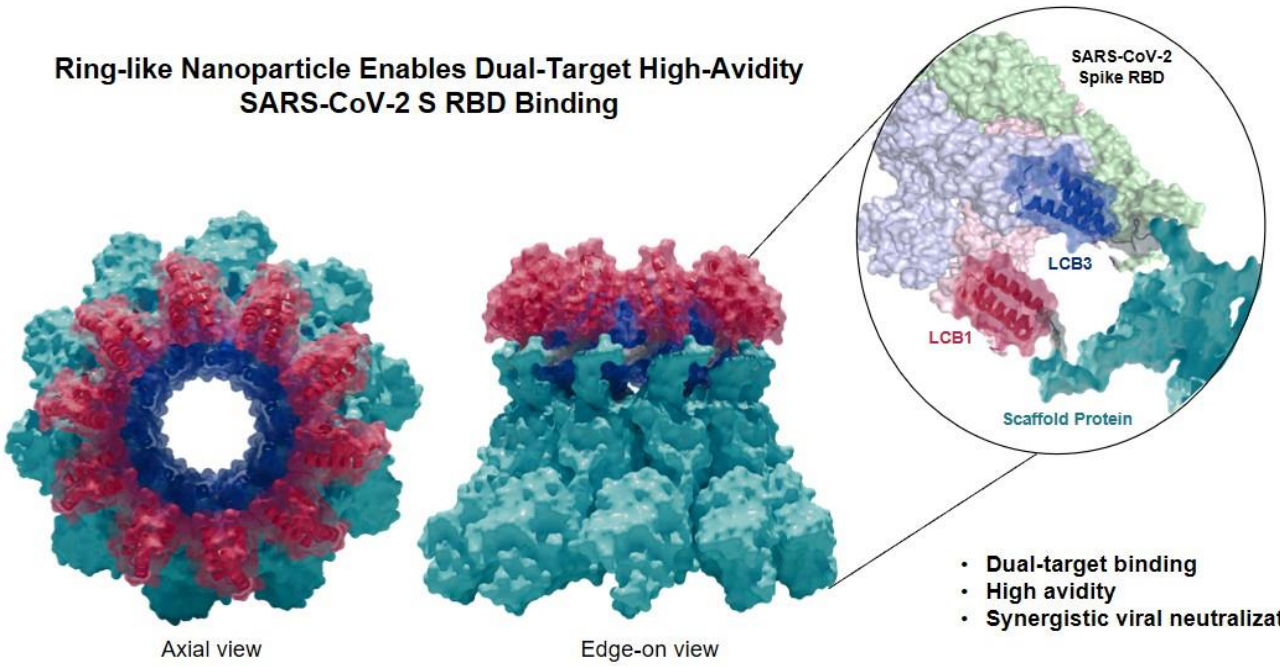
Multivalent Multicomponent Cargo
RLP-S4

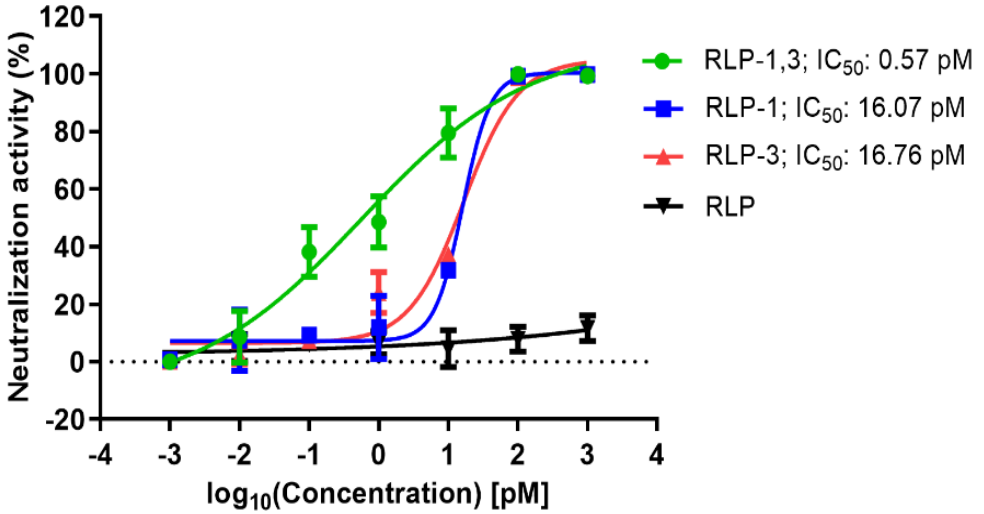


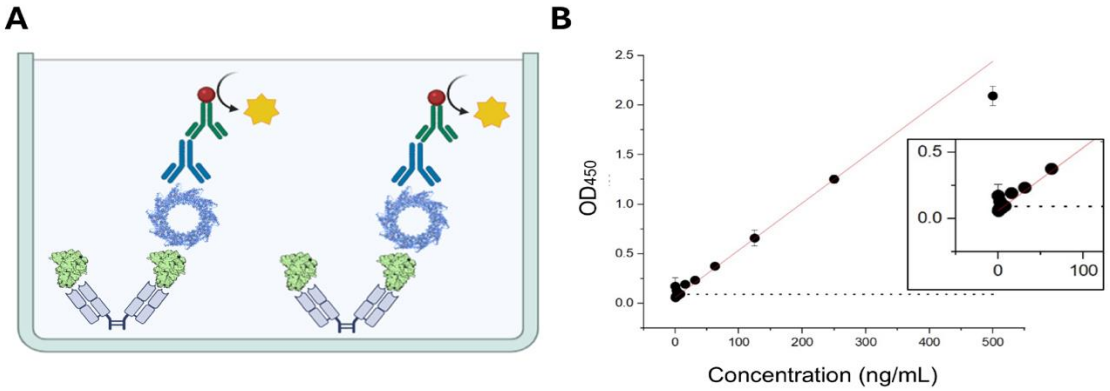
High-density of dual cargoes in 1:1 stoichiometry

- Screened over 10+ RLP-S candidates
- Currently designing 3 additional RLP-S (from non-human pathogens)

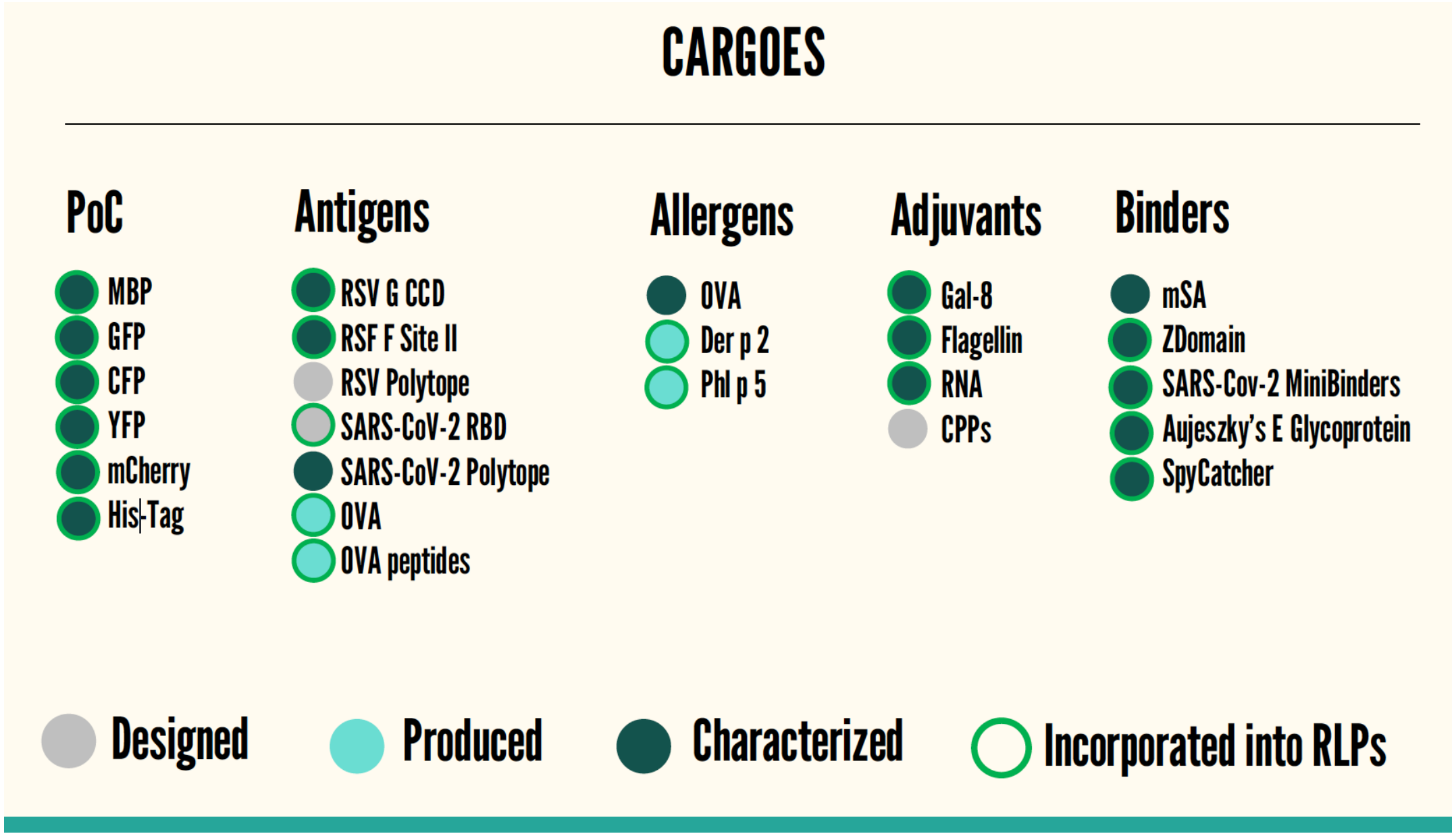
Ring Technology



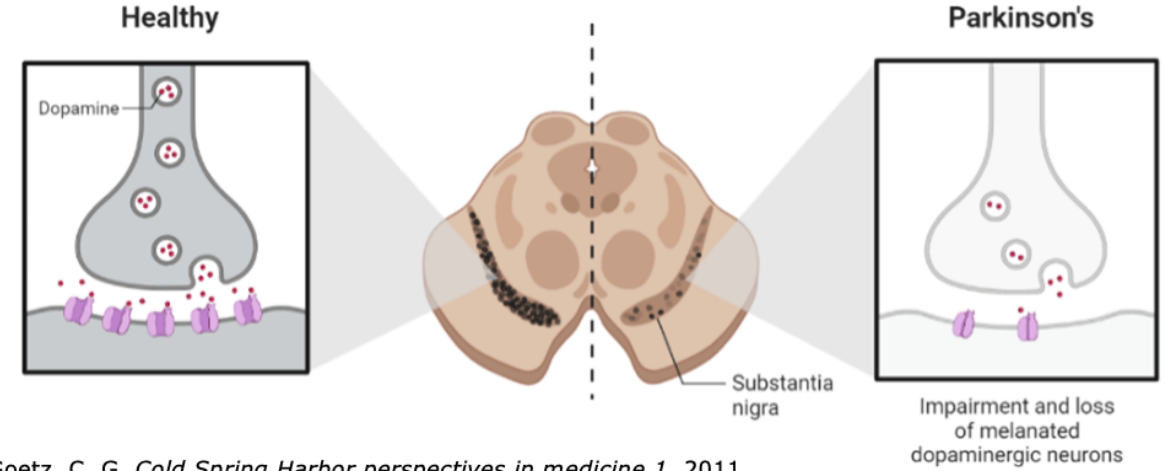




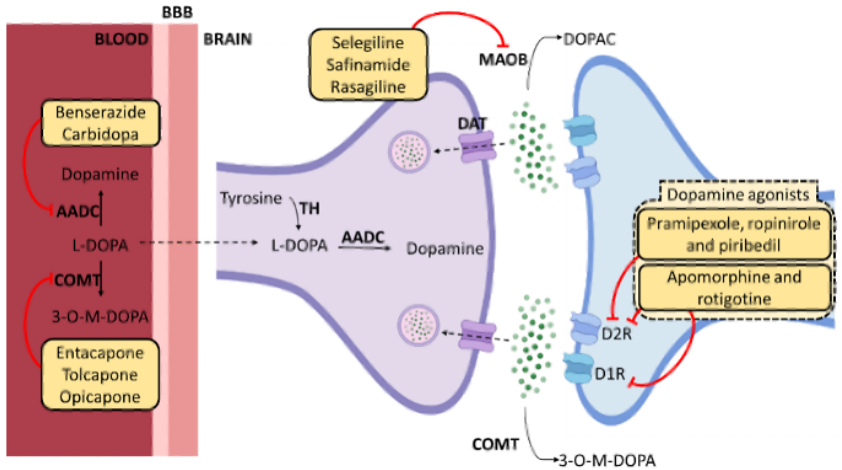
Ring Technology



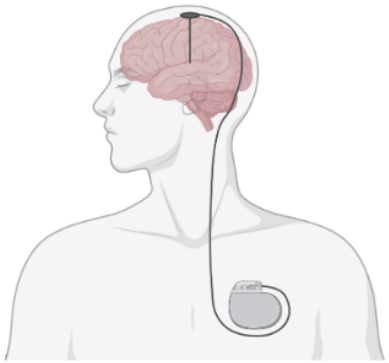
EXAMPLE IV: Therapeutics for Neurodegenerative Diseases



Goetz, C. G. *Cold Spring Harbor perspectives in medicine 1*. 2011, a008862
Lewy, F. *Z. Nervenheilkd*. 1912; 50, 50-55.



Poewe, W. et al. *Nature reviews. Disease primers*. 2017; 3, 17013,



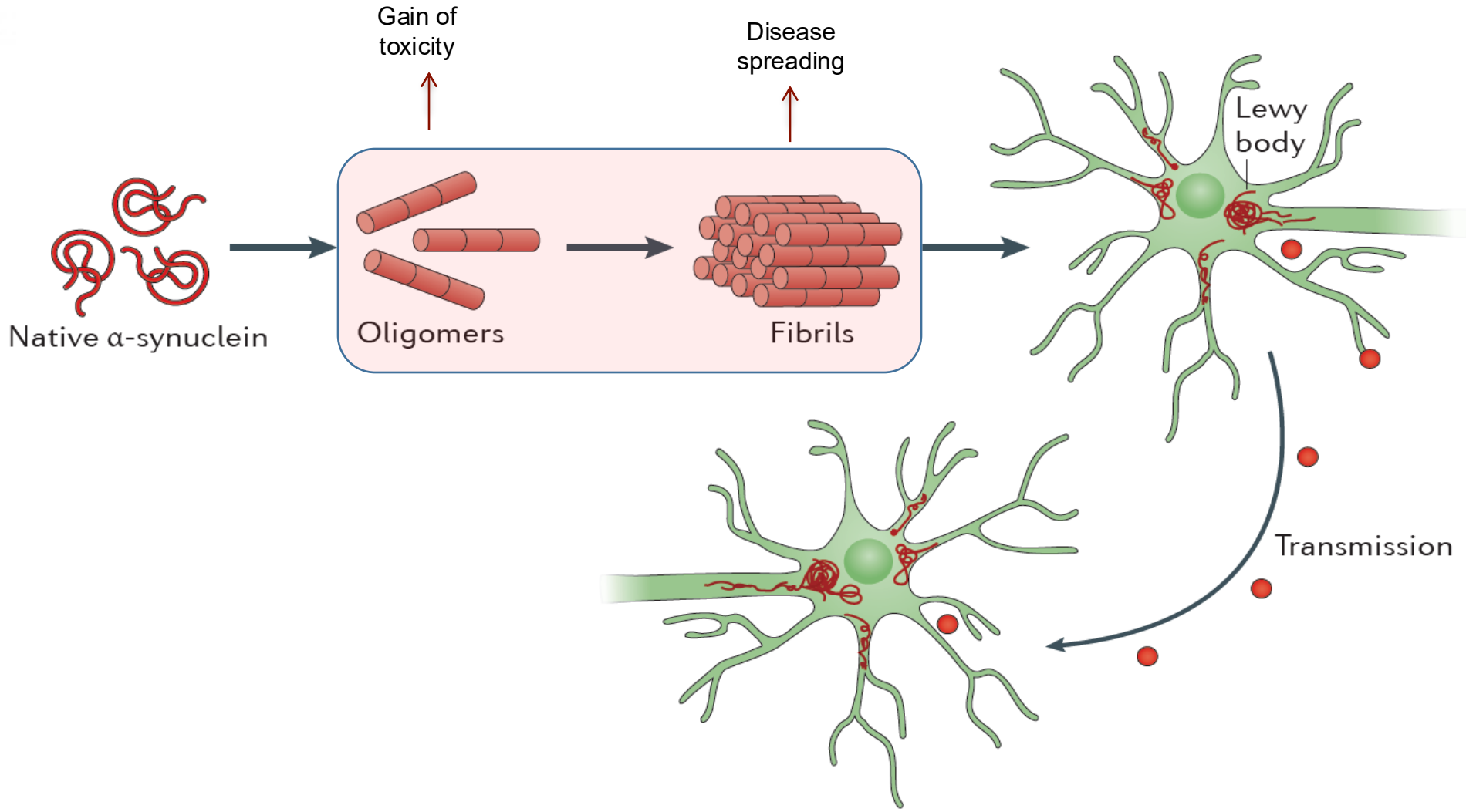
Second most prevalent neurodegenerative disorder worldwide.

Characterised by the **loss of dopaminergic neurons** in the *substantia nigra pars compacta*, and intracellular aggregates: **Lewy bodies and neurites**.

Available therapies are focused on temporary alleviating **symptoms**.

Lack of **effective treatments** that prevents, slow or stop disease progression.

Introduction | α-synuclein as a target in Parkinson's Disease



Can we rationally design a molecule that targets these pathogenic species?

Development of a targeted strategy

nature COMMUNICATIONS

ARTICLE

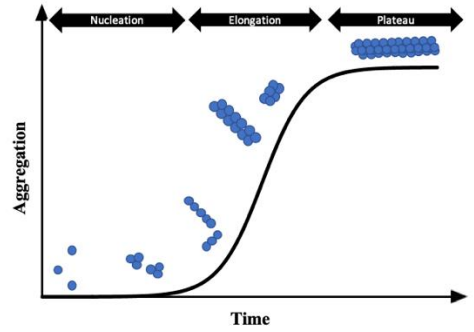
https://doi.org/10.1038/s41467-021-24039-2 OPEN

Check for updates

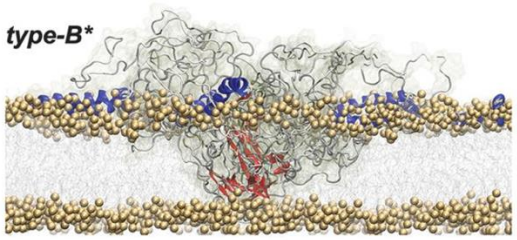
α-Helical peptidic scaffolds to target α-synuclein toxic species with nanomolar affinity

Jaime Santos[1], Pablo Gracia[2], Susanna Navarro[1], Samuel Peña-Díaz[1], Jordi Pujols[1], Nunilo Cremades[2✉], Irantzu Pallarès[1✉] & Salvador Ventura[1✉]

Amyloid progression

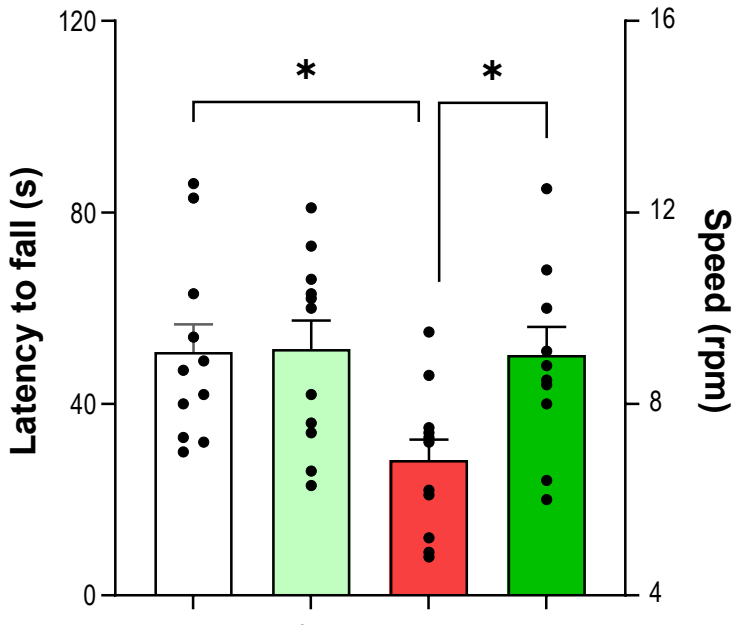


Oligomer associated toxicity



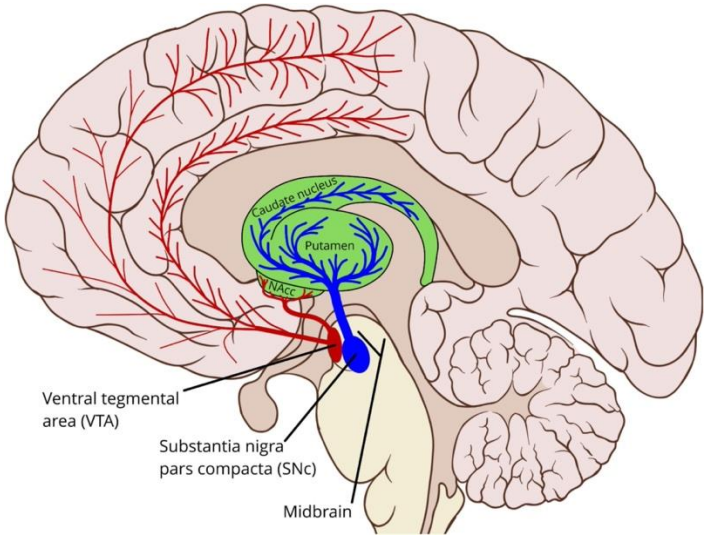
Intranasal Administration

Null + Veh Null + PEPTIDE AAV + Veh AAV + PEPTIDE

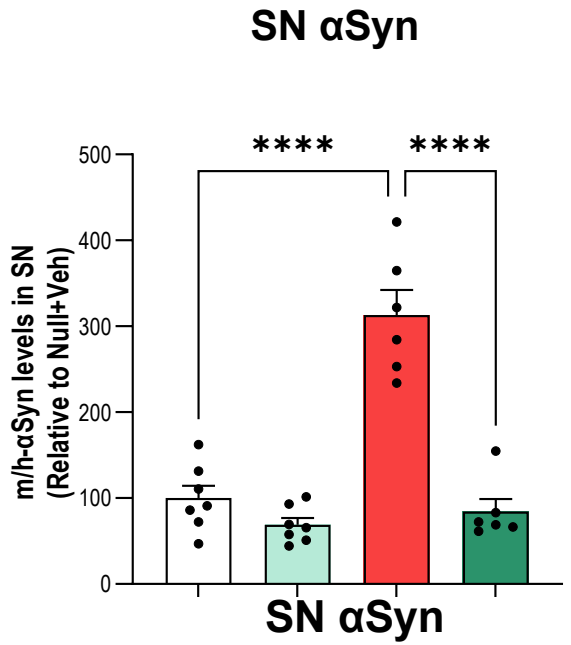


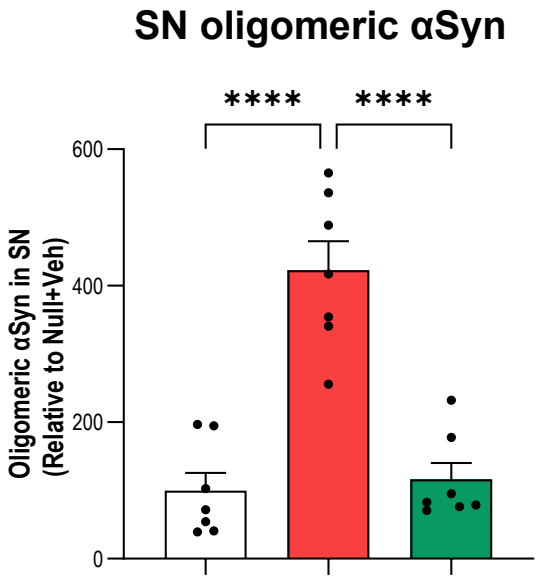
White - Null
Light Green – Null + Peptide
Red - h-asyn
Dark Green - h-asyn + Peptide

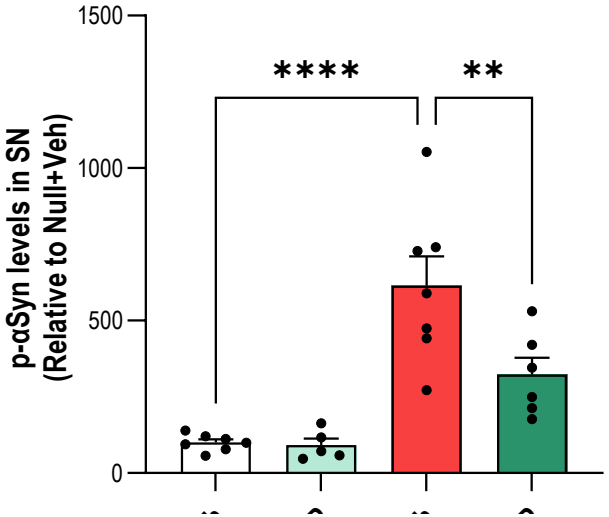
Treatment of a Mice Model of Parkinson's Disease

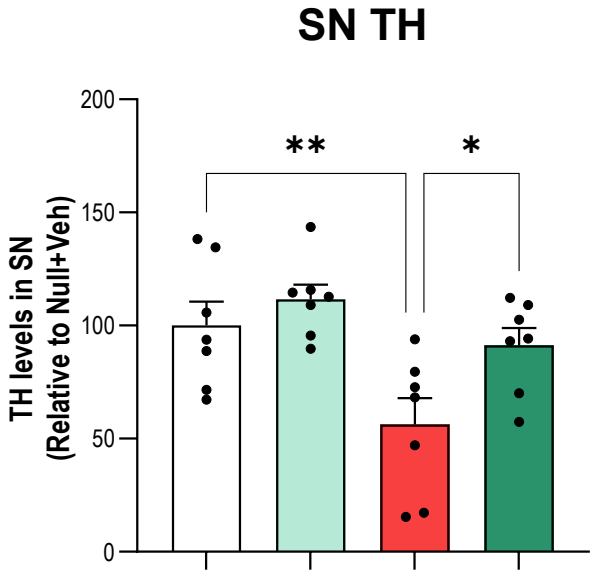


White - Null
Light Green – Null + Peptide
Red - h-asyn
Dark Green - h-asyn + Peptide



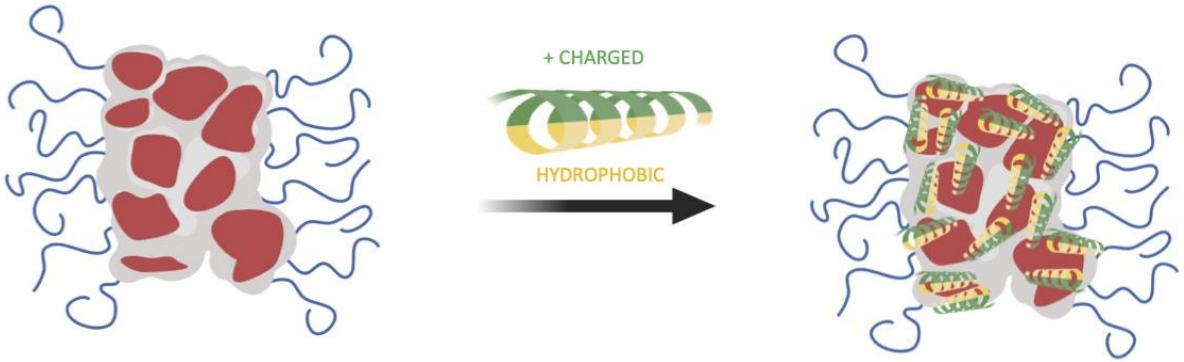




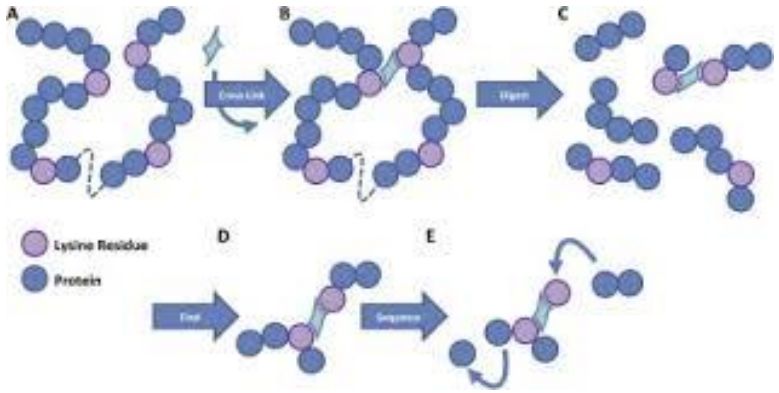


Identification of PSMα3 binding sites

PSMα3 binding sites

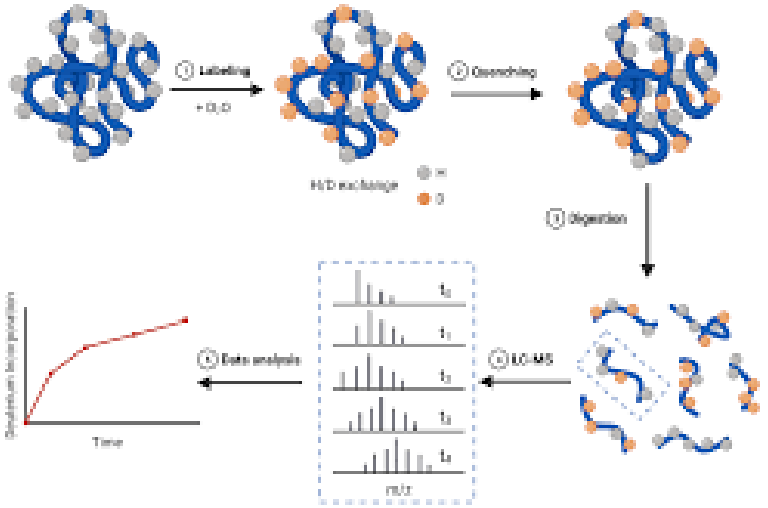


XL-MS



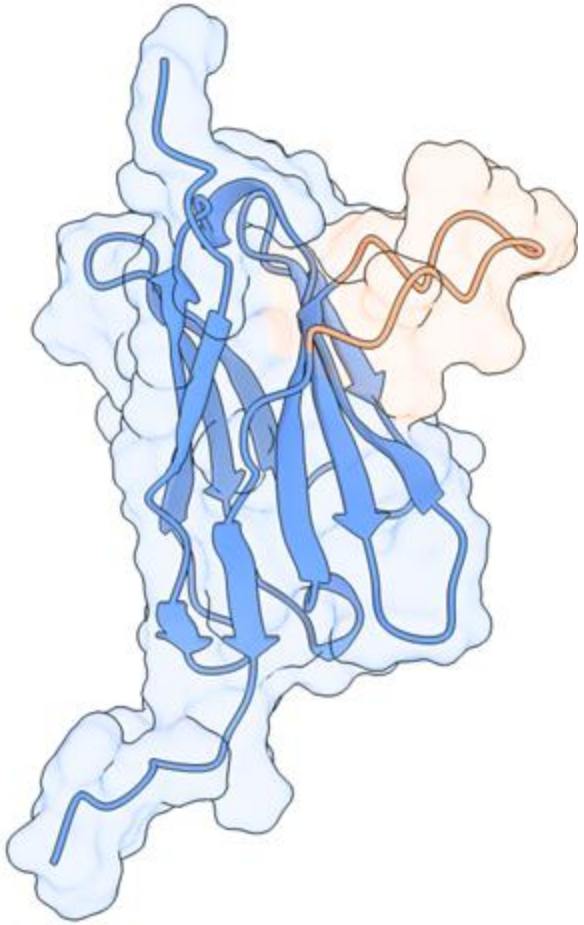
With J.M. Valpuesta

HDX-MS

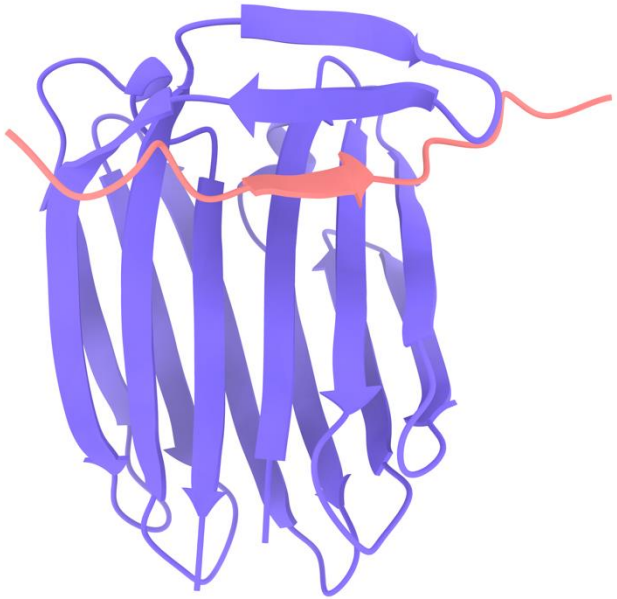


With S. Radford

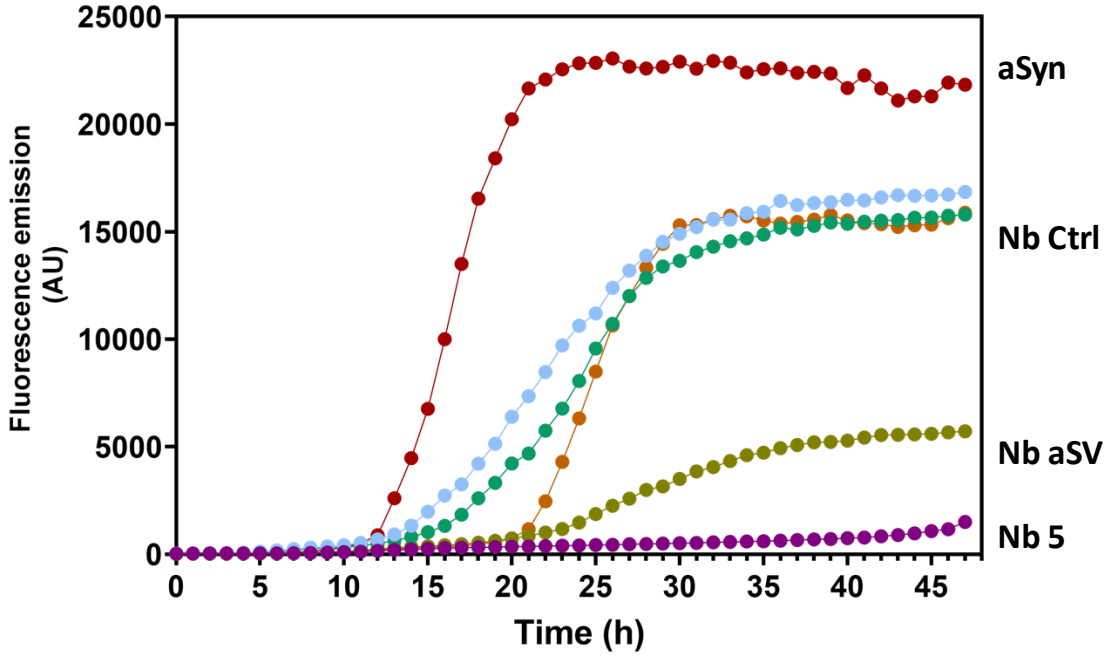
Nanobodies



Nanobodies αSV and Ctrl

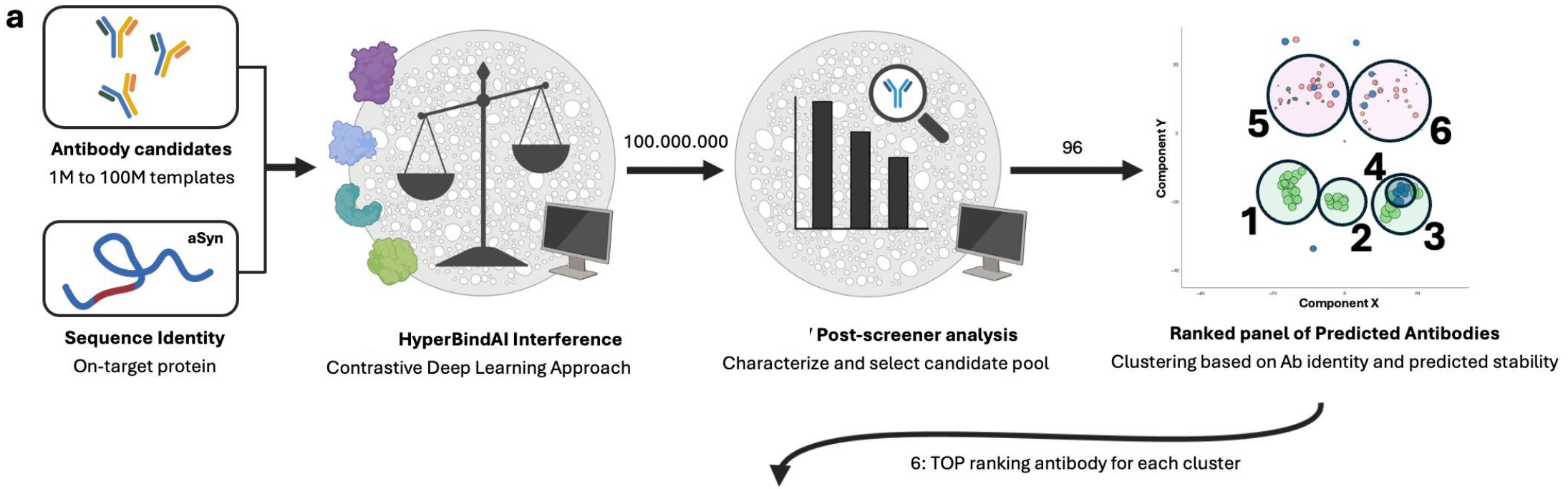


Nanobodies (1-6)



With E. Marcos

AI-guided Design of an Immunotherapy for Parkinson's disease

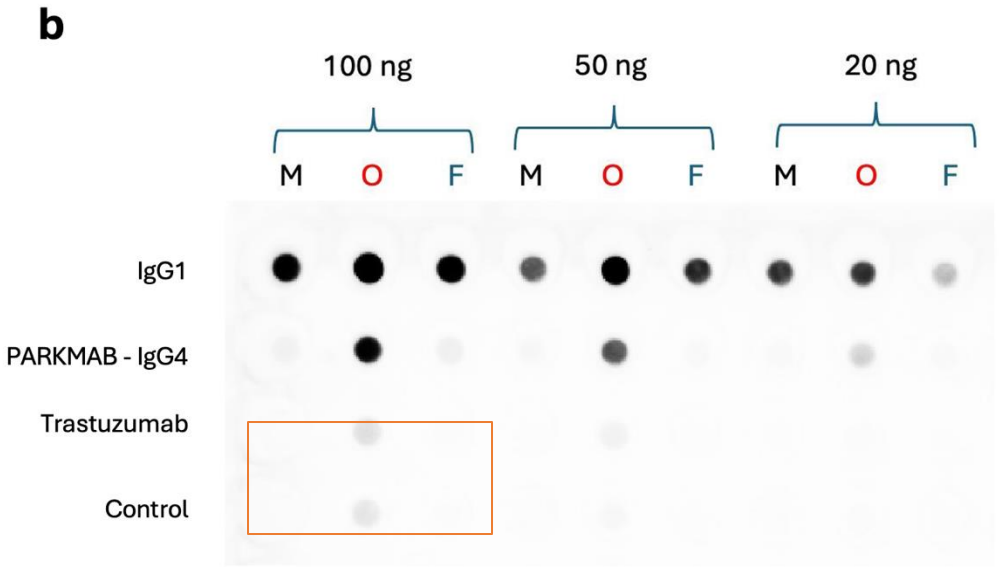


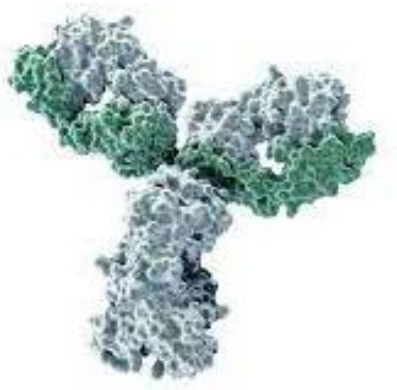
BINDING AND SELECTION OF A HIT CANDIDATE

Recombinant expresion → Purification and yield → aSyn kinetics inhibition → aSO specificity

Towards Immunotherapy for Parkinson's Disease?

Conformational Specificity

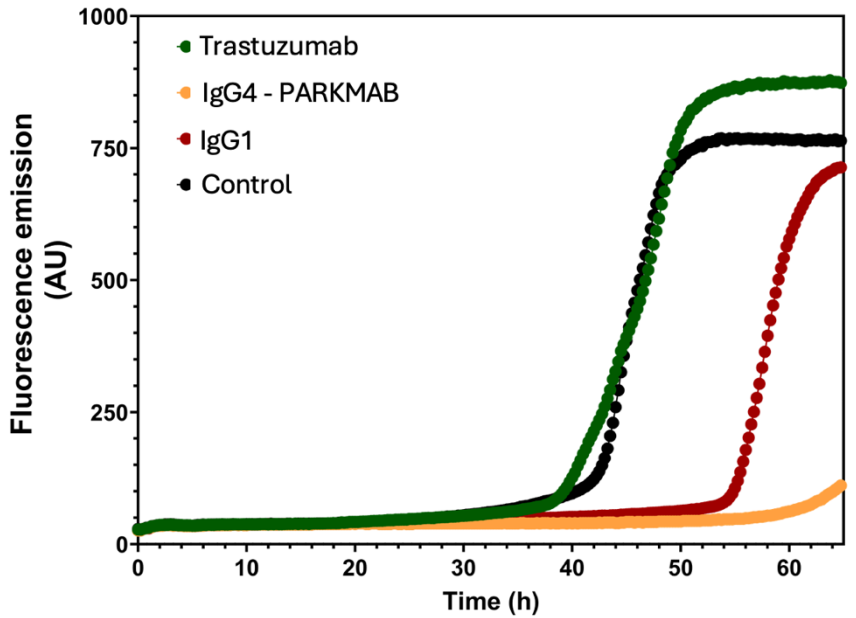




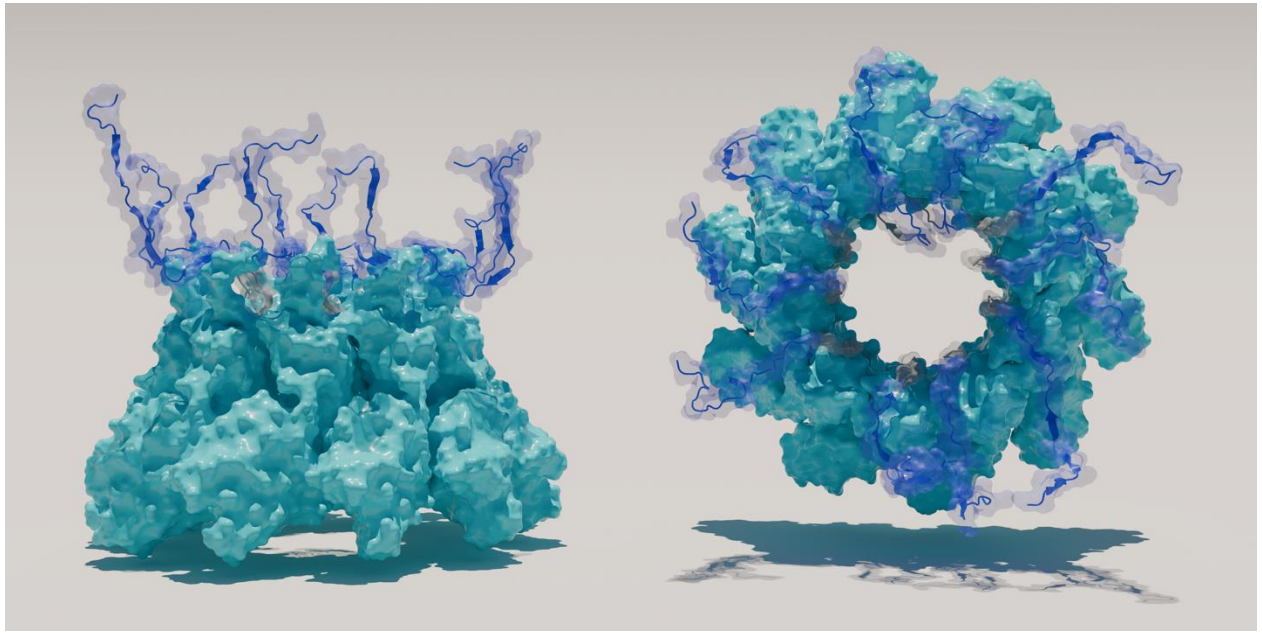
Activity

α-Synuclein/IgG

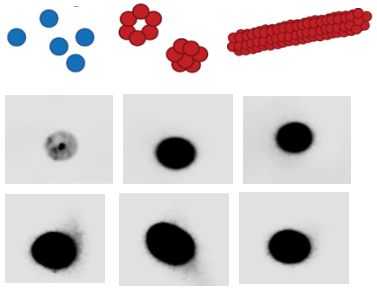
1000/1!!!



Towards Immunotherapy for Parkinson's Disease?



Beyond the State of the Art



- Harnesses the **power** of the **immune system**
- **Unique** conformationally **specific epitope**
- **Structure-guided** & **nanotechnology-driven** vaccine
- Highly **Immunogenic** and **safe**
- **Potent** & **selective antibody** response against **toxic αSyn**

Topics or Fields I Wish to Explore Further

We aim to deepen the rational design of protein-based therapeutics and self-assembling nanomaterials, with applications ranging from targeted immunotherapies and vaccines for neurodegenerative diseases—such as Parkinson’s—to novel platforms in diagnostics and biotechnology.

Ideas for Potential Korea–EU Collaboration under Horizon Europe

We see strong opportunities for joint development of advanced therapeutic and diagnostic solutions by combining our expertise in protein misfolding, structural biology, and bioengineering with Korea’s strengths in nanotechnology, formulation science, and translational medicine.