**Structural basis of membrane disruption and cellular toxicity by α-synuclein oligomers**

Giuliana Fusco1,2, Serene W. Chen1,2, Philip T. F. Williamson3, Roberta Cascella4, Michele Perni1, James A. Jarvis2, Cristina Cecchi4, Michele Vendruscolo1, Fabrizio Chiti4, Nunilo Cremades5, Liming Ying6, Christopher M. Dobson1,\*, Alfonso De Simone2,\*

1Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, UK.

2Department of Life Sciences, Imperial College London, London SW7 2AZ, UK.

3Centre for Biological Sciences and Institute for Life Sciences, University of Southampton, Southampton SO17 1BJ, UK.

4Department of Experimental and Clinical Biomedical Sciences, Section of Biochemistry, University of Florence, 50134 Florence, Italy.

5Biocomputation and Complex Systems Physics Institute (BIFI), Joint Unit BIFI–Instituto de Química Física “Rocasolano” (Consejo Superior de Investigaciones Científicas), University of Zaragoza, 50018 Zaragoza, Spain.

6Molecular Medicine, National Heart and Lung Institute, Imperial College London, London SW7 2AZ, UK.

↵\*Corresponding author. Email: cmd44@cam.ac.uk (C.M.D.); adesimon@imperial.ac.uk **(A.D.)**

**Hide authors and affiliations**

**Science 15 Dec 2017:**

**Vol. 358, Issue 6369, pp. 1440-1443**

**DOI: 10.1126/science.aan6160**

**Abstract**

Oligomeric species populated during the aggregation process of α-synuclein have been linked to neuronal impairment in Parkinson’s disease and related neurodegenerative disorders. By using solution and solid-state nuclear magnetic resonance techniques in conjunction with other structural methods, we identified the fundamental characteristics that enable toxic α-synuclein oligomers to perturb biological membranes and disrupt cellular function; these include a highly lipophilic element that promotes strong membrane interactions and a structured region that inserts into lipid bilayers and disrupts their integrity. In support of these conclusions, mutations that target the region that promotes strong membrane interactions by α-synuclein oligomers suppressed their toxicity in neuroblastoma cells and primary cortical neurons.