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Amyloids in Health and Disease

Edited by Sarah Perrett

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CONTENTS

PREFACE

Misfolding and aggregation of proteins to form amyloid deposits is a characteristic of a number of human diseases, including Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, polyglutamine diseases such as Huntington's, and the prion diseases. Although genetically inherited factors play a role in each of these diseases to a greater or lesser extent, age is also a risk factor, as the manifestation of these diseases reflects a breakdown in the cellular quality control mechanisms that usually ensure that proteins attain and maintain their correctly folded conformations. Understanding the protective mechanisms of the cell, as well as the pathological mechanisms of each of these diseases, is of increasing concern and importance for an aging world population. Interestingly, amyloid aggregates are also found in functional roles in a range of organisms, such as formation of fimbriae (or curli) in bacteria and epigenetic prion-like factors in fungi. Understanding how bacteria, fungi and even mammalian cells can control and utilize protein 'misfolding' to provide biological functions is not only a fascinating biological question, but may also shed light on the pathological mechanisms of amyloid diseases.

Protein folding, misfolding and amyloid formation is no longer considered a specialist subject, of interest only to those carrying out research in this area, but is now a core part of any advanced undergraduate or graduate biochemistry course. It is also a rapidly developing field, with a broad range of approaches being applied, ranging from *in silico* theoretical modelling; via biophysical, biochemical and cellular characterization of molecular mechanisms; to whole organism and systems biology approaches. Importantly, these wide-ranging approaches and techniques are being used in combination to great effect, meaning that research in this area has become truly multi-disciplinary. It is hoped that this volume will provide an accessible overview, highlighting recent progress in this field.

In Chapter 1, Louise Serpell sets the scene by providing an introduction to amyloid structure. The biophysical theme continues in Chapter 2, by Alex Buell, Chris Dobson and Tuomas Knowles, which provides a comprehensive overview of the thermodynamics and kinetics of amyloid fibril formation; and Chapter 3, by Greet De Baets, Joost Schymkowitz and Frederic Rousseau discusses prediction of aggregation prone sequences in proteins. Chapter 4, by Katharina Papsdorf and Klaus Richter, addresses the roles of the protein quality control machinery, particularly molecular chaperones, in health and disease. Chapter 5, by Ko-Fan Chen and Damian Crowther, describes the application of fly models to study amyloid diseases; and Chapter 6, by Barry Panaretou and Gary Jones, discusses yeast models for amyloid disease. Chapters 7–13 provide an overview of research on specific amyloid diseases and the role of key protein players: Chapter 7, by David Allsop and Jennifer Mayes, is focused on amyloid β-peptide in Alzheimer's disease; Chapter 8, by Jian-Zhi Wang and colleagues, focuses on the physiology and pathology of microtubule-associated tau; Chapter 9, by Shun Yu and Piu Chan, addresses the role of α-synuclein in neurodegeneration in the context of Parkinson's disease; Chapter 10, by Nikolai Lorenzen and Daniel Otzen, continues discussion of α-synuclein from the viewpoint of its biophysical properties and cytotoxicity; Chapter 11, by Elizabeth Meiering and colleagues discusses the role of Cu,Zn superoxide dismutase in amyotrophic lateral

sclerosis; Chapter 12, by Erich Wanker and colleagues, addresses polyglutamine disease and aggregation of the protein fragment, Huntingtin exon 1; and Chapter 13, by Jiyan Ma and Fei Wang, discusses prion disease and the 'protein-only hypothesis'. Chapter 14, by Reed Wickner and colleagues, is focused on yeast prions. Finally, in Chapter 15, Margaret Sunde and colleagues give an overview of the many functional roles of amyloids found in Nature.

I would like to thank each author who has contributed to this fascinating collection of articles. I would also like to thank the *Essays in Biochemistry* Editorial Advisory Panel as well as the staff at Portland Press, particularly Clare Curtis, for their guidance and assistance at all stages of this project. Finally, I would like to thank Chris Dobson and Tuomas Knowles for facilitating a 6-month sabbatical in Cambridge, coinciding with the main period of work on this volume.

AUTHORS

Sarah Perrett is a Professor at the Institute of Biophysics (IBP), Chinese Academy of Sciences, where she has been a group leader since 2003. She obtained her undergraduate and Ph.D. degrees from the University of Cambridge, where she then held a Sidney Sussex College Research Fellowship. After a year of full-time Chinese language study at the National University of Singapore, she moved to IBP in 2000, initially supported by fellowships from the Royal Society and the Royal Commission for the Exhibition of 1851. Her current research is supported by the National Natural Science Foundation of China, the Ministry of Science and Technology of China and the Chinese Academy of Sciences. She has returned to Cambridge as a visiting scientist in 2005, 2009 and 2014. Her laboratory is studying the structure and assembly of functional amyloids, and the structure and function of molecular chaperones, using a variety of biochemical and biophysical techniques.

Louise Serpell is a Professor of Biochemistry at the University of Sussex, where she has run a research group looking at the structure of amyloid fibrils since 2003. Previously, she worked at the University of Cambridge and Medical Research Council Laboratory of Molecular Biology in Cambridge where she did much of her early work to visualize the β-sheet structure of amyloid fibrils. She spent 18 months as a postdoctoral researcher at the University of Toronto after completing her D.Phil. in the laboratory of Dr Colin Blake at the University of Oxford, where she worked on the generic structure of the amyloid fibril.

Alexander Buell studied Chemistry and Biochemistry at the University of Tübingen from 2002 to 2004. He was then awarded a 'Sélection Internationale' scholarship to continue his studies at Ecole Normale Supérieure, Paris and the University Paris VI. He graduated in 2007 with a Master's degree in Physical and Theoretical Chemistry. He then did his Ph.D. studies with Professor Sir Mark Welland and Professor Christopher M. Dobson on the kinetics of protein aggregation into amyloid fibrils. In 2011, he was awarded a Thomas Nevile research fellowship from Magdalene College, Cambridge and in 2013, a Leverhulme Trust Early Career Fellowship, both to be held in the Department of Chemistry in Cambridge in order to continue and extend his research on the physical principles and mechanisms underlying amyloid fibril formation.

Christopher Dobson studied Chemistry at the University of Oxford, where he also carried out his Ph.D. work under Robert J.P. Williams on structural characterizations of proteins by the then emerging technique of NMR spectroscopy. He held research fellowships at Merton and Linacre colleges, Oxford and then an Assistant Professorship at Harvard University, before being appointed to a Lectureship in Oxford in 1980, followed by a Readership and Professorship. Until his move to Cambridge in 2001 to take up the John Humphrey Plummer Professorship in Chemical and Structural Biology, his research was mainly directed towards the understanding of protein folding mechanisms, to which he made seminal contributions. Towards the end of the 1990s, he became interested in the link between protein folding and misfolding that can lead to aggregation into amyloid fibrils. His research has contributed groundbreaking fundamental understanding about the causes of protein aggregation and its link with human disorders, such as Alzheimer's disease. Professor Dobson has published more

than 700 scientific articles and has been awarded numerous prizes for his work, most recently, the Heineken prize for Biochemistry and Biophysics.

Tuomas Knowles studied Biology at the University of Geneva and Physics at ETH Zurich. He obtained his Ph.D. in Physics from the University of Cambridge, working at the Cavendish laboratory and Nanoscience Centre with Professor Christopher Dobson, Professor Sir Mark Welland and Professor Cait MacPhee. He then spent time as a St John's College Research Fellow at Cambridge and Harvard University and joined the Department of Chemistry in Cambridge in 2010. His research is focused on the development and application of both theoretical and experimental methods to the study of biological macromolecules, work that has been recognized through a number of prizes, including the British Biophysical Society Medal, Young Investigator Prize and the Royal Society of Chemistry Harrison Meldola Award.

Greet De Baets obtained her Ph.D. in 2013 in the Switch Laboratory (VIB, University of Leuven). She combines computational modelling and cell biological experimentation to investigate the mechanisms of protein aggregation.

Joost Schymkowitz obtained his Ph.D. in 2001 from the University of Cambridge in Professor Sir Alan Fersht's laboratory under the supervision of Laura Itzhaki. He completed his postdoctoral research at the European Molecular Biology Laboratory in Luis Serrano's laboratory. He is now one half of a group leader duo running the Switch Laboratory at the VIB and University of Leuven. The research of the Switch Laboratory combines computational modelling and biophysical and cell biological experimentation to investigate the mechanisms of protein misfolding and aggregation. Specifically, Switch investigates how sequence composition determines the structure of protein aggregates as well as their specificity, their mode of interaction with molecular chaperones and their toxicity to cells.

Frederic Rousseau obtained his Ph.D. in 2001 from the University of Cambridge in Professor Sir Alan Fersht's laboratory under the supervision of Laura Itzhaki. He completed his postdoctoral research at the European Molecular Biology Laboratory in Luis Serrano's laboratory. He is now one half of a group leader duo running the Switch Laboratory at the VIB and University of Leuven. The research of the Switch Laboratory investigates the mechanisms of protein misfolding and aggregation. In order to relate the sequence specificity of aggregation to aggregation-related disease mechanisms, Switch has built an integrated research platform that combines bioinformatics, biophysics, cell biology and now, also increasingly, animal models.

Katharina Papsdorf is a Ph.D. student in Klaus Richter's group. She works on the Hsc70 chaperone system in *Caenorhabditis elegans* and polyglutamine aggregation models in *Saccharomyces cerevisiae*.

Klaus Richter is a group leader at the Technische Universität München. He works on *Saccharomyces cerevisiae* and *Caenorhabditis elegans* model systems to study the function of molecular chaperones and protein misfolding diseases. He is particularly interested in understanding the molecular mechanisms of the chaperones Hsp90 and Hsc70 during their cellular functions. Klaus Richter earned his Ph.D. in the laboratory of Johannes Buchner and completed his postdoctoral studies at Rick Morimoto's Laboratory at Northwestern University.

Ko-Fan Chen is a postdoctoral scientist with a particular interest in using *Drosophila melanogaster* to study neurodegenerative disease and aging, and their impact on circadian biology. His Ph.D. was awarded by Queen Mary University of London where he worked in Ralf Stanewsky's circadian group.

Damian Crowther has a background in clinical neurology and has been working on *in vitro* and *Drosophila*-based models of neurodegenerative diseases for over a decade. He is currently interested in understanding prion-like mechanisms in disorders such as Alzheimer's disease.

Barry Panaretou is a Senior Lecturer within the Institute of Pharmaceutical Science, King's College London (KCL). His primary research interests focus on the function of the Hsp90 chaperone, using yeast as a model organism. Prior to establishing the Yeast Genetics Laboratory at KCL in 2000, he held postdoctoral positions at University College London and the Chester Beatty Laboratory, Cancer Research UK. He obtained his Ph.D. in Biochemistry in 1993 from University College London.

Gary Jones is a Senior Lecturer within the Department of Biology, National University of Ireland Maynooth (NUIM). His primary research interests focus on the influence of chaperone proteins on amyloid formation, using yeast as a model organism. Prior to establishing the Yeast Genetics Laboratory at NUIM in 2004, he held postdoctoral positions at the National Institutes of Health, University College London and University of Wales Swansea. He obtained his Ph.D. in Molecular Biology in 1996 from the University of Liverpool.

David Allsop is a Professor of Neuroscience in the Faculty of Health and Medicine at University of Lancaster. He has more than 30 years of research experience working on the role of β-amyloid in Alzheimer's disease. He was the first person to isolate senile plaque amyloid from frozen post-mortem brain tissue and was one of the founders of the 'amyloid cascade' hypothesis. His current research is focused on the development of biomarkers for neurodegenerative diseases, and on the development of inhibitors of protein aggregation.

Jennifer Mayes is a Research Associate and Senior Teaching Associate in the Faculty of Health and Medicine, University of Lancaster. She has worked with clinicians and patients to set up studies to investigate measures of inhibitory control and working memory as an aid to diagnosis of Alzheimer's disease and other dementias. She now focuses her research on the redox processes associated with β-amyloid aggregation and on the development of inhibitors to target these processes.

Jian-Zhi Wang is a Professor and Director of the Pathophysiology Department, Key Laboratory of Ministry of Education of China for Neurological Disorders, and Deputy Director of the Faculty of Basic Medicine and Research Institutes for Medical Science. Her laboratory is involved in exploring the mechanisms underlying Alzheimer's neurodegeneration, especially the role of the microtubule-associated protein tau. In the search for new strategies to arrest disease progression, the laboratory develops methods, and cell and animal models to measure abnormal tau proteins, and cellular or systemic effects of tau proteins.

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Zhi-Hao Wang is a student in the laboratory of Jian-Zhi Wang working on exploring the mechanisms underlying Alzheimer's neurodegeneration.

Shun Yu obtained his Ph.D. in 1998 from Shiga University of Medical Science in Japan. After a 2 year postdoctoral position in the Academy of Military Medical Sciences of China, he moved to the Department of Neurobiology, Beijing Institute of Geriatric Medical and Research Center, Xuanwu Hospital, Capital Medical University. Since then, he has focused on the study of Parkinson's disease, especially the pathogenic mechanism and diagnostic biomarkers.

Piu Chan graduated from Hunan Medical College in 1983 followed by clinical postgraduate training at the First Affiliated Hospital (Xiangya Hospital). He received his Ph.D. in Neuroscience from Sun Yat-Sen University of Medical Science in 1990, followed by a 2 year postdoctoral position at the Parkinson's Institute in California. Dr Chan was then the Director of the Molecular Genetics Laboratory at the Parkinson's Institute until he returned to China in 2000. Since then, he has been Professor of Neurology, Geriatrics and Neurobiology at the Beijing Institute of Geriatric Medical and Research Center and Xuanwu Hospital of Capital Medical University in Beijing. He has focused on studies of Parkinson's and related diseases, especially epidemiology, genetics, biomarkers and animal models.

Nikolai Lorenzen obtained his B.Sc. degree in Civil Engineering (Biotechnology) from Aalborg University in 2008. He was then enrolled as an M.Sc. student in Peptide and Protein Chemistry at Stockholm University for 1 year until he was enrolled as a Ph.D. student under the supervision of Daniel Otzen. He finished his Ph.D. in November 2013, working on the topic of α-synuclein aggregation and the use of small-molecule drugs to inhibit this process. He now works as a Research Scientist in protein biophysics at Novo Nordisk.

Daniel Otzen is Professor of Nanobiotechnology at the Interdisciplinary Nanoscience Center (iNANO) at Aarhus University. He obtained his Ph.D. at Aarhus University in 1995 after protein folding studies in Professor Sir Alan Fersht's laboratory at the University of Cambridge. He has also worked as a staff scientist at Novozymes within the field of stability and folding of industrial enzymes. His interests include pathological and functional amyloid formation, the structures and properties of pre-fibrillar species, approaches to prevent aggregation and oligomer formation and also the folding and stability of membrane proteins. He is a member of the Danish Royal Society of Sciences and Letters.

Helen Broom is a Ph.D. candidate at the University of Waterloo, working under the supervision of Elizabeth Meiering. She began her graduate studies in 2008, after completing a B.Sc. in Biochemistry and Biotechnology at the University of Waterloo. Her graduate research is on characterizing folding, misfolding and aggregation of metal-free forms of SOD1.

Jessica Rumfeldt obtained her Ph.D. on stability and folding mechanisms of SOD1 in 2006 from the University of Waterloo under the supervision of Elizabeth Meiering. She was a postdoctoral research fellow at the University of Waterloo and then the University of California San Diego under the supervision of Dr James R. Halpert and Dr Dimitri R. Davydov, investigating substrate binding co-operativity in cytochrome P450s. She is now a Research Associate studying various proteins including SOD1 in the Meiering group.

Elizabeth Meiering completed her Ph.D. on the folding and function of barnase with Professor Sir Alan Fersht at the University of Cambridge in 1992. Her postdoctoral research used NMR to analyse the roles of mutations and hydration on dihydrofolate reductase, with Professor Gerhard Wagner at Harvard Medical School. Since joining the University of Waterloo in 1996, her group's research has focused on the folding, misfolding and design of numerous proteins of fundamental, medical or biotechnological interest. She has held a John Charles Polanyi Award and University Research Chair, and has served on the ALS Society of Canada Scientific Advisory Board, as Associate Dean of Graduate Studies, and on the Editorial Board for Protein Engineering Design and Selection.

Philipp Trepte is currently doing his Ph.D. in the laboratory of Erich Wanker, working on the systematic generation and characterization of a protein interaction map of synaptic proteins. During his Master's degree in Cell Biology at the University of Osnabrück, he visited the

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Nadine Strempel is working towards her Ph.D. in Erich Wanker's laboratory with a focus on the molecular mechanisms of huntingtin aggregation and its modulation by small molecules. Before coming to the Max Delbrück Center, she completed a diploma degree with a thesis in Molecular Biology and Virology at the Department of Applied Tumor Virology of the German Cancer Research Center. To deepen her knowledge in Immunology and Biochemistry, she studied one semester abroad at the University of Copenhagen.

Erich Wanker is Chair of Molecular Medicine at Charité University Medicine Berlin and heads the Neuroproteomics research group at the Max Delbrück Center for Molecular Medicine Berlin-Buch. He graduated in Chemical Engineering and Biochemistry from the University of Technology Graz, where he also completed his Ph.D. in 1992. After a postdoctoral fellowship at the University of California, Los Angeles he became a group leader at the Max-Planck-Institute for Molecular Genetics and was appointed to his present positions in 2001. His research interests are in protein misfolding and neurodegeneration, molecular mechanisms of protein–protein and protein–drug interactions and on high-throughput network biology.

Jiyan Ma received training in Medicine and studied leukaemia viruses at the Shanghai Medical University. He received his Ph.D. degree in 1997 from the University of Illinois. Dr Ma started to study prion disease when he was a postdoctoral fellow in Dr Susan Lindquist's laboratory at the University of Chicago. Ma started his group at Ohio State University in 2002 and continued to study the pathogenic mechanism of prion disease. Currently, he is a Professor at the Center for Neurodegenerative Science and Head of the laboratory of prion mechanisms in neurodegeneration at the Van Andel Research Institute.

Fei Wang received his B.Sc. degree from Nankai University. He joined Dr Jiyan Ma's laboratory and started his Ph.D. thesis research on prion disease in 2003. Dr Wang's graduate work focused on the biochemical characterization of interactions between recombinant PrP and lipids. Dr Wang's current research interests lie in molecular mechanisms of prion infectivity. Dr Wang has co-authored 14 peer-reviewed articles on prion research, including one invited methodology paper and one invited review article, and he is the recipient of the Alberta Prion Research Institute International Young Researcher Prize.

Reed Wickner majored in Mathematics at Cornell University and obtained his MD from Georgetown University. After studying yeast RNA viruses, he discovered, in 1994, that the non-chromosomal genes [URE3] and [PSI+] are yeast prions of Ure2p and Sup35p. He is currently interested in expanding knowledge of the in-register parallel β-sheet prion amyloid structure, the mechanisms by which prions cause disease in yeast, the means by which Btn2p and Cur1p cure the [URE3] prion, and the mutability of the prion cloud.

Herman Edskes obtained his Ph.D. at the University of Kentucky studying plant pararetroviruses with Professor Robert Shepherd. He carried out postdoctoral work with Dr Reed Wickner at the National Institutes of Health investigating viruses and prions of the yeast *Saccharomyces cerevisiae*. Currently, he is a staff scientist at the National Institute of Diabetes, Digestive and Kidney Diseases in the Laboratory of Biochemistry and Genetics and focuses on yeast prions.

David Bateman obtained his Ph.D. from the University of Toronto in the department of Medical Biophysics. He is currently investigating the cloud of prion variants, using yeast as a model system.

Amy Kelly is currently a postdoctoral fellow in the Wickner laboratory at the National Institutes of Health. She acquired her Ph.D. from the University of Illinois, Urbana-Champaign in the laboratory of Dr Jan Novakofski, where she studied population genetics of mammalian prion diseases. Her current research focuses on elucidating the molecular ecology of yeast prions.

Anton Gorkovskiy is a visiting fellow in the Laboratory of Biochemistry and Genetics, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. Dr Gorkovskiy obtained his Ph.D. in Biochemistry in 2009 from the Institute of Biochemistry and Physiology of Microorganisms, Russian Academy of Sciences. Working in Dr Tatyana Kalebina's group, Dr Gorkovskiy was investigating *Saccharomyces cerevisiae* cell wall proteins possessing amyloid properties. Currently, he is studying metastable and toxic *S. cerevisiae* prion variants and working on determining the fine structure of amyloid fibrils formed by one of the prion-forming proteins, Sup35.

Yaron Dayani is currently a postdoctoral fellow in the Wickner laboratory at the National Institute of Diabetes and Digestive and Kidney Diseases. He completed his Ph.D. studies at the Faculty of Life Sciences, The Hebrew University of Jerusalem, in collaboration with Dr Simchen and the Lichten laboratory at the National Cancer Institute, where he studied activities responsible for the resolution of double Holliday junctions. Before that, he completed his undergraduate and Master's studies in Genetics with a focus on aging using nematode models in the Gruenbaum laboratory. His present research focuses on prion propagation using yeast as a model.

Albert Zhou graduated with a B.Sc. in Biochemistry and Molecular Biology from the University of Maryland, Baltimore County and is currently a post-baccalaureate fellow working with Dr Reed Wickner. Zhou is investigating the prion-forming ability of various proteins.

Chi Pham joined Professor Roberto Cappai's laboratory in the Department of Pathology at The University of Melbourne, working on amyloid diseases associated with neurodegeneration, specifically on Alzheimer's disease and Parkinson's disease following the completion of her Ph.D. Currently located in the Discipline of Pharmacology at The University of Sydney, her research focus is now on the role of amyloid-forming fungal hydrophobin proteins in rice blast infections.

Ann Kwan received her Ph.D. in Biochemistry from the University of Sydney. After working as an Australian postdoctoral fellow, she took up the position of NMR Facility Manager at the School of Molecular Bioscience, University of Sydney. She is currently a research fellow at the School as well as being responsible for the NMR facility. Her research focuses on investigations of protein structures and functions, and protein assemblies including functional amyloids. Ann has received Young Investigator Awards from the East Coast Protein Meeting, Lorne Protein Conference, ISMAR and AMZMAG societies.

Margaret Sunde received her Ph.D. in Biochemistry from the University of Cambridge. Her interest in amyloid was sparked during her postdoctoral work with Colin Blake and Chris Dobson in Oxford, where she focused on structural and biophysical studies of disease-associated amyloid fibrils and the role of protein misfolding in amyloid formation. Now a senior lecturer at the University of Sydney, Sunde's research efforts have turned to the study of functional amyloid, particularly the formation and biological application of amyloid formed by the fungal hydrophobin proteins.

ABBREVIATIONS

AA	arachidonic acid
AAA ATPases	ATPases associated with various cellular activities
ACE	angiotensin-converting enzyme
AD	Alzheimer's disease
ADAM	a disintegrin and metalloproteinase
ADDL	amyloid β-derived diffusible ligand
ADF	*Araneusdiadematus* fibroin
aDrs	anionic dermaseptin
AD-tau	abnormally hyperphosphorylated tau from AD brain
AFM	atomic force microscopy
AGE	advanced glycation end product
ALS	amyotrophic lateral sclerosis
ANS	8-anilinonaphthalene-1-sulfonic acid
APH-1	anterior pharynx defective 1
APOE	apolipoprotein E
apoSH	metal-free disulfide-reduced monomer
apoSS	metal-free disulfide-intact dimer
APP	amyloid precursor protein
APR	aggregation-prone region
Aβ	amyloid β-peptide
Aβ42	amyloid β-peptide 42-residue fragment
BACE1	β-site amyloid precursor protein cleaving enzyme 1
BBB	blood–brain barrier
BSE	bovine spongiform encephalopathy
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase II
CASA	chaperone-assisted selective autophagy
CCS	copper chaperone for SOD-1
CCT	chaperone-containing T-complex protein
CDK	cyclin-dependent kinase
CFTR	cystic fibrosis transmembrane conductance regulator
CHIP	C-terminus of the heat-shock cognate 70-interacting protein
CK1	casein kinase 1
CMA	chaperone-mediated autophagy
CNS	central nervous system
CPEB	cytoplasmic polyadenylation element-binding protein
CSPα	cysteine string protein α
Cu,Zn-SOD1	copper/zinc superoxide dismutase 1
CWD	chronic wasting disease
DA	dopamine
DAT	dopamine transporter

DIC	dynein intermediate chain
DISC	death-inducing signalling complex
DLS	dynamic light scattering
DSC	differential scanning calorimetry
dSTORM	direct stochastic optical reconstruction microscopy
DYRK1A	dual-specificity tyrosine-phosphorylation-regulated kinase 1A
ECE	endothelin-converting enzyme
EGCG	(−)-epigallocatechin gallate
EM	electron microscopy
ER	endoplasmic reticulum
ERK	extracellular-signal-regulated kinase
fAD	familial Alzheimer's disease
fALS	familial amyotrophic lateral sclerosis
FAP	familial amyloid polyneuropathy
FRET	Förster resonance energy transfer
FTDP-17	frontotemporal dementia with Parkinsonism-linked to chromosome-17
FTLD	frontotemporal dementia lobar degeneration
FUS	fused-in-sarcoma
GA	geldanamycin
GFP	green fluorescent protein
GndHCl	guanidine hydrochloride
GndSCN	guanidinium thiocyanate
GPI	glycosylphosphatidylinositol
GPx	glutathione peroxidase
GSK-3	glycogen synthase kinase 3
GWAS	genome-wide association study
HD	Huntington's disease
HDAC6	histone deacetylase 6
3-HK	3-hydroxykynurenine
holoSS	mature, fully metallated and disulfide-intact dimer
Hsc70	heat-shock cognate 70 stress protein
Hsp	heat-shock protein
HSPB1	heat-shock 27 kDa protein 1
5-HT	serotonin
HTT	huntingtin
HTTex1	huntingtin exon 1
IAPP	islet amyloid polypeptide
IB	inclusion body
IDE	insulin-degrading enzyme
IDP	intrinsically disordered polypeptide
iLBD	incidental Lewy body disease
IPOD	insoluble protein deposit
iPS	induced pluripotent stem

ITC	isothermal titration calorimetry
JNK	c-Jun N-terminal kinase
KLC	kinesin light chain
KMO	kynurenine 3-monooxygenase
KPI	kunitz-type protease inhibitor
LB	Lewy body
LN	Lewy neurite
LRP	low-density lipoprotein receptor-related protein
M	folded monomer
β2M	β_2-microglobulin
MAPK	mitogen-activated protein kinase
MARK	microtubule affinity-regulating kinase
MASS	Mutant Aggregation and Stability Spectrum
MAT	monoamine transporter
MBD	microtubule-binding domain
MCI	mild cognitive impairment
mHTT	mutant HTT
NAC	nascent chain-associated complex or non-amyloid β-peptide component
NBD	N-terminal ATP-binding domain
NCC	nucleated conformational conversion
NCP	10-[4′-(N-diethylamino)butyl]-2-chlorophenoxazine
NE	norepinephrine
NEF	nucleotide exchange factor
NET	norepinephrine transporter
NFT	neurofibrillary tangle
NMDA	*N*-methyl-D-aspartate
NMDAR	*N*-methyl-D-aspartate receptor
OPTN	optineurin
PAR1	partitioning defective 1
PASTA	Prediction of Amyloid STructure Aggregation
PD	Parkinson's disease
PDPK	proline-directed protein kinase
PE	phosphatidylethanolamine
PEN-2	presenilin enhancer 2
PFD	prion-forming domain
PHF	paired helical filament
PICALM	phosphatidylinositol-binding clathrin assembly protein
PiD	Pick's disease
PIMA	Peptide Interaction Matrix Analyzer
Pin1	peptidylprolyl *cis–trans* isomerase NIMA-interacting 1
PI-PLC	phosphoinositide-specific phospholipase C
PK	proteinase K
PMCA	protein misfolding cyclic amplification

polyQ	polyglutamine
POPG	1-palmitoyl-2-oleoyl-*sn*-glycero-3-phospho-(10-rac-glycerol)
PP2A	protein phosphatase 2A
PrP	prion protein
PrP^{C}	normal cellular prion protein
PrP^{Sc}	disease-specific conformation of prion protein
PSP	progressive supranuclear palsy
PSSM	position-specific scoring matrix
QCM	quartz crystal microbalance
QUIN	quinolinic acid
RAC	ribosome-associated complex
RAGE	receptor for advanced glycation end products
recPrP	recombinant PrP
RHIM	RIP homotypic interaction motif
RIP	receptor-interacting protein
ROS	reactive oxygen species
sALS	sporadic amyotrophic lateral sclerosis
SALSA	Simple ALgorithm for Sliding Averages
SAXS	small-angle X-ray scattering
SBD	substrate-binding domain
SEC	size-exclusion chromatography
SERT	serotonin transporter
SH3	Src homology 3
sHsp	small heat-shock protein
SNAP-25	25 kDa synaptosome-associated protein
SNARE	soluble *N*-ethylmaleimide-sensitive fusion protein-attachment protein receptor
SOD1	superoxide dismutase 1
SR	sepiapterin reductase
SSA	senile systemic amyloidosis
SSP	secretion signal peptide
SUMO1	small ubiquitin-like modifier protein 1
αsyn	α-synuclein
TBP	TATA-binding protein
TCP	T-complex protein
TDP-43	transactive response DNA binding protein 43
TG	transglutaminase
TH	tyrosine hydroxylase
ThT	thioflavin-T
TIRF	total internal reflection fluorescence microscopy
TMAO	trimethylamine N-oxide
TriC	TCP1-containing ring complex
TPR domain	tetratricopeptide domain
TREM2	triggering receptor expressed on myeloid cells 2

TSE	transmissible spongiform encephalopathy
TTR	transthyretin
UPR	unfolded protein response
UPS	ubiquitin–proteasome system
vCJD	variant Creutzfeldt–Jacob disease
VMAT2	vesicular monoamine transporter 2
WT	wild-type