BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Eisenberg, David

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard College, Cambridge, MA (J.T. Edsall)	A.B.	06/1961	Biochemical Sciences
Oxford University, Oxford, UK (C.A. Coulson)	D. Phil.	10/1964	Theoretical Chemistry

A. Personal Statement

Understanding biology and disease has been my career-long interest. Starting with biochemistry, computation and x-ray diffraction, I later added the tools of TEM, micro-electron diffraction, and cryoEM. I have focused increasingly on proteins associated with neurodegeneration. These are diseases of protein fibril formation and oligomerization. Applying newly developed methods of microcrystallography, cryoEM, and microelectron diffraction, our lab has determined the atomic structures of some 200 of disease related fibril structures. In the past 4 years, we have determined structures of two dozen amyloid fibrils by cryoEM, including those associated with Alzheimer's, Parkinson's, diabetes type 2, transthyretin amyloidosis, and ALS. On the basis of structures, we have designed inhibitors that halt amyloid fibril formation, and halt the spread of fibrils from cell to cell.

Recently we (Seidler et al. Nature.Comms https://doi.org/10.1038/s41467-022-32951-4) have applied our structures to discovery small-molecules that disaggregate fibrils from Alzheimer's brains into benign fragments. This work demonstrates the potential for structure-based drug discovery for neurodegenerative diseases, of the type that has been so successful in finding drugs to treat cancer and metabolic conditions. This method has also produced

In laboratory training, I have supervised dozens of undergraduates, over 180 Ph.D. theses and postdoctoral fellows, most of who are carrying out research in structural and computational biology in universities, research institutes, and industries. Former lab members work in at least a dozen countries. I have coauthored ~400 research papers and reviews, and two books: a monograph on the structure and properties of water [>5000 citations], still in print after 50 years, and a text on physical chemistry for the life sciences.

I established a user-friendly facility for determination of atomic structures by x-ray and EM methods which has welcomed and helped scores of users from UCLA, other research institutions and industry.

Ongoing and recently completed projects that I would like to highlight include:

1R01AG070895
Eisenberg (PI)
02/01/22 – 01/31/27
Towards Treatment of Alzheimer's Disease by Targeting Pathogenic Tau and Beta-Amyloid Structures

1RF1AG065407
Kayed (PI); Role: Co-investigator
07/01/21 – 06/31/26

B. Positions, Scientific Appointments, and Honors

Paul Boyer Chair of Molecular Biol.		2009-present	
Howard Hughes Medical Institute	Investigator	2001-2023	Investigator
UCLA, Los Angeles	Director	1993-2014	UCLA-DOE Institute
UCLA, Los Angeles	Asst. Prof-Prof	1969-present	Chem & Biochem, Biol. Chem.
Caltech, Pasadena	Postdoc	1966-1969	Structural Biology (R.E. Dickerson)
Princeton University, Princeton	Postdoc	1964-1966	Water, H-bonding (Walter Kauzmann)

Selected Memberships and Awards
Passano Laureate, 2020, NAS Strategic Planning Committee, 2019; Paul Sigler Prize, Yale University, 2017; Vallee Visiting Professor, 2016; UCSF Andrew Braisted Award Lecturer, 2016; ASBMB Bert and Natalie Vallee Award in Biomedical Science, 2015; Fellow, American Crystallographic Assoc, 2015, MBI Legacy Award, 2015; Inaugural Switzer Price for Biomedical Discovery, 2014; ISMB Accomplishment by a Senior Scientist Award, 2013; Honorary Fellow, Queen's College, Oxford, 2010; Biophysical Society, Emily Gray Award, 2009; Harvey International Prize in Human Health, 2009; Harvard Westheimer Medal, 2005; UCLA Seaborg Medal, 2004; American Philosophical Society, 2003; Institute of Medicine 2002; Amgen Award of the Protein Society, 2000; Fellow, Biophysical Society Inaugural Year Fellow, 1999; American Chemical Society Repligen Award in Molecular Biology, 1998; Protein Society Stein & Moore Award, 1996; Pierce Award of the Immunotoxin Society, 1992; American Academy of Arts & Sciences, 1991; National Academy of Sciences, 1989; UCLA Faculty Research Lectureship, 1989; Guggenheim Fellowship, 1985; McCoy Award of the UCLA Department of Chemistry and Biochemistry for innovative research, 1982 (with R.E. Dickerson); UCLA Distinguished Teaching Award, 1975; USPHS Career Development Award, 1972-1977; Alfred P. Sloan Fellowship, 1969-1971; Rhodes Scholarship, 1961-1964; L.J. Henderson Prize, 1961 for best undergraduate thesis in Biochemical Sciences.

C. Contributions to Science Google Scholar citations n = 112,000; h=149

1. Structural biology of the amyloid state of proteins: Prior to our atomic-resolution crystallographic studies of amyloid-forming proteins, only low-resolution information from EM and fiber diffraction were available. Papers a, b, and c describe the common spine of amyloid fibers: a pair of beta-sheets, closely mating by interdigitation of their sidechains, termed a steric zipper. Paper a was the first atomic resolution structure of the amyloid state. Paper b showed that numerous amyloid fibrils have steric-zipper spines, and classified the possible symmetries of this structural motif. Paper c reports reveals a new type of protein interaction—termed LARKS—between low-complexity domains, responsible for multivalent networks and gels, such as those found in membrane-less organelles. Paper d reports the unexpected discovery that amyloid fibrils in post mortem brains of patients clinically and pathologically certified as FTLD-TDP have amyloid fibrils of the C-terminal domain of a lysosomal protein TMEM106B, rather than the expected TDP-43.

a. Nelson R, Sawaya MR, Balbirnie M, Madsen AO, Riekel C, Grothe R, Eisenberg D. Structure of the cross-beta spine of amyloid-like fibrils. *Nature.* **435**, 773-8 (2005). PMCID: PMC1479801 [~2400 citations]
b. Sawaya MR, Sambashivan S, Nelson R, Ivanova MI, Sievers SA, Apostol MI, Thompson MJ, Balbirnie M, Wiltzius JJ, McFarlane HT, Madsen AØ, Riekel C, Eisenberg D. Atomic structures of amyloid cross-beta spines reveal varied steric zippers. *Nature.* **447**, 453-7 (2007). PMID: 17468747 [~2300 citations]
c. Michael P. Hughes, Michael R. Sawaya, David R. Boyer, Lukasz Goldschmidt, Jose A. Rodriguez, Duilio Cascio, Lisa Chong, Tamir Gonen, David S. Eisenberg. Atomic structures of low-complexity

protein segments reveal kinked β-sheets that assemble into networks. *Science.* **359***, 698-701* (2018). PMCID: PMC6192703

d. Yi Xiao Jiang, Qin Cao, Michael R. Sawaya, Romany Abskharon, Peng Ge, Michael DeTure, Dennis W. Dickson4, Janine Y. Fu, Rachel R. Ogorzalek Loo, Joseph A. Loo, David S. Eisenberg. Amyloid fibrils in FTLD-TDP are composed of TMEM106B and not TDP-43. Nature, 605, 304 (2022).

2. Inhibition of formation of amyloid fibrils and of amyloid cytotoxicity: Dozens of human diseases are associated with amyloid fibrils. We have been able to inhibit amyloid formation both by structure-based design (papers e-h). Papers g and h report improved inhibitors and disaggregants of tau fibrils (at the root of Alzheimer's, CTE, and 25 other tauopathies) and of the intercellular prion-like spread of tau fibrils.

e. Sievers SA, Karanicolas J, Chang HW, Zhao A, Jiang L, Zirafi O, Stevens JT, Munch J, Baker D, Eisenberg D. Structure-based design of non-natural amino-acid inhibitors of amyloid fibril formation. *Nature.* **475**, 96-100 (2011). PMCID: PMC4073670 [461 citations]

f. Saelices L, Chung K, Lee JH, Benson MD, Bijzet J., Cohn W, Whitelegge, JP, Eisenberg D. Amyloid seeding of transthyretin by ex vivo cardiac fibrils: inhibition and implications, *PNAS*, **115**:E6741-E6750, (2018). www.pnas.org/cgi/doi/10.1073/pnas.1805131115

g. Seidler PM, Boyer DR, Murray KA, Yang TP, Bentzel M, Sawaya MR, Rosenberg G, Cascio D, Williams CK, Newell K, Ghetti B, DeTure MA, Dickson D, Vinters HV, Eisenberg DS* Structure-based inhibitors halt prion-like seeding by Alzheimer's disease– and tauopathy-derived brain tissue samples J. Biol. Chem, in press (2019)

h. Paul M. Seidler, Kevin A. Murray, David R. Boyer , Peng Ge , Michael R. Sawaya, Carolyn J. Hu, Xinyi Cheng, Romany Abskharon, Michael A. DeTure, Christopher K. Williams, Dennis W. Dickson, Harry V. Vinters, & David S. Eisenberg. Structure-based discovery of small molecules that disaggregate Alzheimer's disease tissue derived tau fibrils in vitro, Nature Comms. https://doi.org/10.1038/s41467-022-32951-4 (2022)

3. Computational analysis of amino acid sequences and protein structures: As protein sequences and structures became readily available in the 1980s and 1990s, I developed new methods to extract information from sequences and structures. Paper i describes a new property of proteins—the hydrophobic moment, which has been widely applied to detect periodicities in proteins. Paper j introduced atomic solvation parameters, used subsequently by many to estimate free energy changes of protein folding and binding. Paper k introduced the Profile method for detection of distantly related protein sequences. It was later coded by others into the powerful PsiBlast algorithm. Paper l invented threading of sequences on to structures to identify new proteins having previously determined folds. This method has also been widely applied.

i. D Eisenberg, RM Weiss, TC Terwilliger. The hydrophobic moment detects periodicity in protein hydrophobicity. *Proc. Natl. Acad. Sci. U.S.A.* **81**, 140-144 (1984). PMCID: PMC344626 [1131 citations]

j. D. Eisenberg, A.D. McLachlan. Solvation energy in protein folding and binding. *Nature.* **319**,199-203 (1986). PMID: 3945310 [2352 citations]

k. M Gribskov, AD McLachlan, D Eisenberg. Profile analysis: detection of distantly related proteins. *Proc. Natl. Acad. Sci. U.S.A.* **84**, 4355-4358 (1987). PMCID: PMC305087 [1763 citations]

l. JU Bowie, R Luthy, D Eisenberg. A method to identify protein sequences that fold into a known 3D structure. *Science.* **253**, 164-170 (1991). PMID: 1853201 [3458 citations]

4. Methods for inferring protein interactions and functions from genome sequences. The advent of genome sequencing brought the puzzle of how to infer from this mass of information the function of proteins and the pathways and complexes formed by proteins. Our group, together with the group of Todd Yeates, worked out several methods described in papers m, n, and o. We also began a database of protein interactions described in paper o.

m. Marcotte EM, Pellegrini M, Ng HL, Rice DW, Yeates TO, Eisenberg D. Detecting protein function and protein-protein interactions from genome sequences. *Science.* **285**, 751-3 (1999). PMID: 10427000 [2163 citations]

n. Marcotte EM, Pellegrini M, Thompson MJ, Yeates TO, Eisenberg D. A combined algorithm for genome-wide prediction of protein function. *Nature.* **402**, 83-6 (1999). PMID: 10573421 [1181 citations]
o. Xenarios I, Salwínski L, Duan XJ, Higney P, Kim SM, Eisenberg D. DIP, the Database of Interacting Proteins: a research tool for studying cellular networks of protein interactions. *Nucleic Acids Res.* **30**, 303-5 (2002). PMCID: PMC99070 [2038 citations]

5. Electron microscopy and micro-electron diffraction:

p. Frank J, Goldfarb W, Eisenberg D, Baker TS. Reconstruction of glutamine synthetase using computer averaging. [The first report of TEM single particle averaging] *Ultramicroscopy*. **3**, 283-90 (1978). PMCID: PMC4167717 [277 citations]
q. Jose A. Rodriguez, Magdalena Ivanova, Michael R. Sawaya, Duilio Cascio, Francis Reyes, Dan Shi, Smriti Sangwan, Elizabeth Guenther, Lisa Johnson, Meng Zhang, Lin Jiang, Mark Arbing, Julian Whitelegge, Johan Hattne, Brent Nannega, Aaron S. Brewster, Marc Messerschmidt, Sébastien Boutet, Nicholas K. Sauter, Tamir Gonen, David Eisenberg. Structure of the toxic core of α-synuclein from invisible crystals *Nature.* **525**, 486-90 (2015). PMCID: PMC4791177 [498 citations]
r. Michael R. Sawaya, Jose Rodriguez, Duilio Cascio, Michael J. Collazo, Dan Shi, Francis E. Reyes, Johan Hattnef, Tamir Gonen, David S. Eisenberg. Ab Initio structure determination from prion nanocrystals at atomic resolution by MicroED *PNAS*, **113**, 11232-11236 (2016). 9. PMCID: PMC5056061 [89 citations]
s. de la Cruz, M. Jason; Hattne, Johan; Shi, Dan; Seidler, Paul; Rodriguez, Jose; Reyes, Francis; Sawaya, Michael R.; Cascio, Duilio; Weiss, Simon C.; Kim, Sun Kyung; Hinck, Cynthia S.; Hinck, Andrew P.; Calero, Guillermo; Eisenberg, David; Gonen, Tamir Atomic-resolution structures from fragmented protein crystals with the cryoEM method MicroED *Nature Methods.* **14**, 399-402 (2017). PCMID: PMC5376236 [130 citations]