BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Cheng, Xinyi

eRA COMMONS USER NAME (credential, e.g., agency login): XINYICHENG

POSITION TITLE: Ph.D. Candidate

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California, Los Angeles	B.S.	06/2018	Biochemistry
University of California, Los Angeles	Ph.D.	In progress	Molecular Biology

A. Personal Statement

I am a Ph.D. candidate at University of California, Los Angeles, and my current research is focused on using structural methods to study pathological amyloid aggregates and their bio-complexes.
My passion for the biological sciences was cultivated in my undergraduate research experience. I was an undergraduate researcher at **Dr. Anne Andrews**'s laboratory. My main project was to study the developmental influence of serotonin transporter (SERT) on behavior. This resulted in an undergraduate thesis that focused on my efforts to design and optimize a mice behavior test to measure anxiety behavior. I also helped develop fast-scan-cyclic voltammetry (FSCV) methods for measuring serotonin level in mice brains *in vivo*. In these projects I applied rigorous experimental design and cutting-edge technology to solve relevant scientific problems regarding antidepressants and anxiety.
In my graduate studies, I am working at the lab of **Dr. David Eisenberg**, a world-renowned biochemist and biophysicist. Dr. Eisenberg and his lab provide extensive mentoring in a collaborative and intellectually stimulating environment. My technical training focuses on structural biology methods like x-ray crystallography and cryo-EM. Our lab studies the structural basis for conversion of normal proteins to the amyloid state. Specifically, I would like to elucidate the structure of patient-derived, pathological amyloid aggregates in complex with therapeutic macromolecules like antibodies. I am excited about applying the newest technological advances in the field of structural biology to tackle challenging complex structures; and ultimately these structures will provide insights into how to develop novel therapeutics that interacts strongly with their targets.
In addition to my research, I am honing my science teaching and mentoring skills by mentoring younger students in lab and in the graduate program, and being a teaching assistant in undergraduate courses. I also regularly communicate my research progress in group meetings, student seminars and poster sessions.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2016 - 2018 Undergraduate researcher, University of California, Los Angeles
2012 - Graduate Student Research Assistant, University of California, Los Angeles

Other Experience and Professional Memberships

2019-2022 Mentor, MBIDP Peer Mentorship Program

Honors

2022-23	Whitcome Pre-Doctoral Fellowship Awardee
2021	FASEB Poster prize, Protein Aggregation Conference: Function, Dysfunction and Disease
2021	2021 APS Student Poster Prize, Advances in COVID-19 Prevention and Treatment Enabled by Structural Biology Research, APS/CNM 2021
2021	2020-2021 Sigman Symposium Best Poster award
2018-2019	UCLA Graduate Dean's Scholar Award
2018	UCLA Department of Chemistry and Biochemistry Departmental Honors
2018	UCLA Semel Institute for Neuroscience and Human Behavior Undergraduate Student Research Conference Outstanding Poster Award
2017-2018	UCLA Honorary Undergraduate Research Scholarship Program Award
2017	UCLA Whitcome Summer Undergraduate Research Fellowship
2014-2017	UCLA Dean's Honor List

C. Contributions to Science

1. Undergraduate Research: During my time as an undergraduate researcher at Dr. Anne Andrews's lab at UCLA, we are interested in studying the effect of prenatal exposure to serotonin-selective reuptake inhibitor (SSRI) on mice behavior and neurochemistry in adulthood. For behavioral studies, I adopted and optimized a test measuring anxiety behavior called novelty suppressed feeding test and calibrated the test for use in our lab. During this process, I learnt about how to assure reproducibility in behavioral data by implementing good experiment design. To study mice neurochemistry, our lab developed an in house FSCV setup that is capable of measuring changes in neurotransmitters like dopamine and serotonin real-time in mice brains as they are alive and moving. I helped prepare the experimental apparatus and train the mice to get used to the experimental procedure.

a. Movassaghi, C.; Perrotta, K.; Yang, H.; Iyer, R.; **Cheng, X.;** Dagher, M.; Alcaniz, M.; Andrews, A. (2021) Simultaneous serotonin and dopamine monitoring across timescales by rapid pulse voltammetry with partial least squares regression. *Anal. Bioanal. Chem.*

b. Andrews, A. M.; **Cheng, X.;** Altieri, S. C.; Yang, H. (2017) Bad behavior: Assuring reproducibility in behavior data. *ACS Chem. Neurosci.*

2. Graduate Research: Dr. David Eisenberg's lab focuses on using structural biology to elucidate amyloid protein structure and design inhibitors of amyloid toxicity using structure-based approaches. In lab, my projects oriented towards tau, a protein heavily implicated in amyloid aggregation in Alzheimer's disease. I had extensive experience working recombinant tau and also patient brain-derived tau amyloid aggregates. Using my expertise in tau protein, I have assisted in projects that aim to design various types of inhibitors for tau amyloid aggregation. My main project is a structural study of tau amyloid fibrils in complex with macromolecules. This project is on-going and I hope to submit a first author publication in the next year.

a. Murray, K. A.; Hu, C. J.; Griner, S. L.; Pan, H.; Bowler, J. T.; Abskharon, R.; Rosenberg, G. M.; **Cheng, X.;** Seidler, P. M.; Eisenberg, D. S. De novo designed protein inhibitors of amyloid aggregation and seeding. *PNAS.*

b. Murray, K. A.; Boyer, D. R.; Seidler, P. M.; Ge, P.; Sawaya, M. R.; Hu, C. J.; **Cheng, X.**; Abskharon, R. A.; Pan, H.; DeTure, M. A.; Williams, C. K.; Dickson, D. W.; Vinters, H. V.; Eisenberg, D. S. Structure-based discovery of small molecules that disaggregate tau fibrils from Alzheimer's disease. *Nature Communications.* (In review)

D. Additional Information: Research Support and/or Scholastic Performance

Scholastic Performance

YEAR	COURSE TITLE	GRADE
UNIVERSITY OF CALIFORNIA, LOS ANGELES (UNDERGRADUATE)		

YEAR	COURSE TITLE	GRADE
2014	Chemical Structure	A+
2014	Differential & Integral Calculus	A
2015	Energetics & change	A
2015	Calculus of Several Variables	A
2015	General Chemistry Lab	A
2015	Organic Chemistry I	A+
2015	Integration & Infinite Series	A
2015	Differential Equations	A
2015	Mechanics	A-
2015	General Chemistry Lab 2	A
2015	Organic Chemistry II	B+
2015	Calculus of Several Variables II	A
2015	Oscillations & Waves & Fields	A-
2016	Biomedical research Concepts	A
2016	Organic Chemistry Lab 1	B+
2016	Organic Chemistry III	B+
2016	Cells & Tissues & Organs	B+
2016	Structure & Enzymes & Metabolism	A
2016	Lab & Scientific Method	A-
2016	Electrodynamic & Optics	A+
2016	Lab – Electricity & Magnetism	A
2016	Intro – Molecular Biology	A
2016	Biomedical Research Skills	A
2016	Physics – Thermodynamics	A+
2016	Biochemical Methods I	A-
2016	Genetics	A-
2017	DNA & RNA & Protein Synthesis	A
2017	Physical Biochemistry	A
2017	Biomedical Ethics	A
2017	Metabolism & Regulation	B
2017	Biochemical Methods II	A-
2017	Behavioral Neuroscience	A
2017	Computers in Chemistry	A
2018	Biology of Cells	A
2017-2018	Directed Research	A+

UNIVERSITY OF CALIFORNIA LOS ANGELES (GRADUATE)

2018	Dynamic Macro Assembly	A
2018	Mitochondria Disease	A-
2019	Structural Molecular Biology	A
2019	Structural Molecular Biology Lab	A
2019	Scientific Writing	A
2019	Protein Mass Spectrum	A
2019	Ethics – Biomedical Research	S

BIOGRAPHICAL SKETCH

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NAME: Eisenberg, David

eRA COMMONS USER NAME (credential, e.g., agency login): EISENBERG2

POSITION TITLE: Paul D. Boyer Professor of Biochemistry & Molecular Biology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

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 amyloid and prion diseases. These are diseases of protein oligomerization and fibrillation. By newly developed methods of microcrystallography and microelectron diffraction, our lab has been able to determine the atomic structures of some 200 of disease related fibril structures. In the past 5 years, we have determined structures of ~30 amyloid fibrils by cryoEM.

In laboratory training, I have supervised dozens of undergraduates, over 160 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:

MICHAEL J FOX FOUNDATION 05/17/2021 – 05/16/22 1.00 calendar months
Grant ID: MJFF-001166 $147,720 Total
Completion of Preclinical Study of a Safe and Effective Image-based Biomarker for Parkinson's Disease particles
To develop a non-radioactive diagnostic that can in principle detect the development of Parkinson's disease by MRI. This repeatable diagnostic will also enable studies of patients over time, necessary for evaluating the effectiveness of therapies.

MICHAEL J FOX FOUNDATION(PI: Sally Fraustchy)01/01/2021 – 06/30/22 1.00 calendar months
Grant ID: MJFF-001065 $82,221.55 Total
Liganded Nanoparticles to Inhibit Alpha-synuclein (aSyn) Aggregate Deficits in Endosomal-Lysosomal and Autophagy
Genetic and sporadic Parkinson's disease (PD) cases implicate dysfunction in the endo-lysosomal

system, autophagy-lysosomal protein degradation and lysosomal biogenesis. The overarching goal is to determine whether these highly specific peptides show efficacy inPD models.

MCB 1616265 (Eisenberg) 09/01/2016 – 08/31/2022 0.20 calendar months
NSF $414,335 Total
Reversible Amyloid-Like Fibrils in Membraneless Organelles
To explore the full variety of interactions and assembly states found in membrane-less organelles by mapping the human reversible amylome.

R01 AG048120 (Eisenberg) 06/01/2019 – 05/31/2024 1.50 calendar months
NIH/NIA $1,950,000 Total
Development of Inhibitors and Diagnostics for Systemic Amyloid Diseases
We aim to further our understanding of amyloid structure, and apply this understanding to the development of new and better candidate therapeutics and diagnostics.

RF1AG065407 (Diamond) 09/15/2020 – 08/31/2024 0.50 calendar months
Seeds and Strains Derived from Tau Monomer $303,145 Total
We will oversee the characterization of tauopathy-derived brain fibrils using cryo-electron microscopy (cryoEM). His group will create micro-crystals of subdomains (i.e. local structures) of the tau protein for x-ray crystallography. This will be used to test predictions made by cross-linking mass spectrometry and other biophysical studies performed in the Joachimiak lab.

1RF1AG065407 (Kayed) 07/01/2021 – 06/31/2026 1.50 calendar months
NIH $939,220 Total
Interdisciplinary Research Network on Biologically Active Tau Aggregate Polymorphs from Alzheimer's Disease and Related Dementias
The Eisenberg lab will prepare oligomeric specimens for structural studies, including cryo-EM. Antibodies and nanobodies will be prepared for aids in specimen preparation. Cryo-EM and crystallographic structural determinations will be carried out.

1R01AG070895 (Eisenberg) 02/01/22 – 01/31/27 4.00 calendar months
NIH $1,068,649 Total
Towards Treatment of Alzheimer's Disease by Targeting Pathogenic Tau and Beta-Amyloid Structures
To develop effective drugs, we take the approach that has been effective for treating cancer and HIV-AIDS: structure-based drug design by applying the powerful tools of electron microscopy and x-ray diffraction.

HHMI (Eisenberg) 09/01/18 – 08/31/23 0 calendar month
Howard Hughes Medical Institute
General Support of the Eisenberg laboratory, including salaries for PI (Eisenberg), Crystallographer, and Laboratory Manager, and Administrative Assistant.

B. Positions, Scientific Appointments, and Honors

Paul Boyer Chair of Molecular Biol.		2009-present	
Howard Hughes Medical Institute	Investigator	2001-present	Investigator
UCLA, Los Angeles	Director	1993-2014	UCLA-DOE Institute
UCLA, Los Angeles	Asst. Prof-Prof	1969-present	Chemistry & Biochemistry
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

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

C. Contributions to Science >109,000 citations, <h> = 148

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 the first identification by cryoEM structures of pathogenic fibrils of protein TM106B in the disease FTLD-TDP. Paper d 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.

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 [~2300 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 [~2260 citations]
c. Jiang, Y.X., Cao, Qin, Sawaya, M.R.…Eisenberg, D.S. Amyloid fibrils in disease FTLD-TDP are composed of TMEM106B not TDP-43. Nature (2022)
d. 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 [248 Citations]

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 of the aggregation of tau (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 [444 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, Rodriguez,JA, Sawaya,MR, Cascio,D, Murray,K, Gonen,T, Eisenberg,DS.. Structure-based inhibitors of tau aggregation. *Nature Chemistry*. **10**, 170-176 (2018). DOI:10.1038/NCHEM.2889 (2017). PMCID: PMC5784779 [175 Citations]

h. 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*, **294**(44):16451-16464. DOI 10.1074/jbcRA119.009688

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** [1117 citations]

j. D. Eisenberg, A.D. McLachlan. Solvation energy in protein folding and binding**.** ***Nature.*** **319,199-203 (1986). PMID: 3945310** [2330 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** [1748 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 [3366 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 [2148 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 [1183 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 [2018 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 [279 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 [468 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 [83 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 [128 citations]

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Boyer, David

eRA COMMONS USER NAME (credential, e.g., agency login): davboyer

POSITION TITLE: Postdoctoral Scholar

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Michigan, Ann Arbor, MI	BS	12/2014	Biochemistry
University of California, Los Angeles, Los Angeles, CA	PhD	06/2021	Structural Biology
University of California, Los Angeles, Los Angeles, CA	Postdoctoral Scholar	07/2021 – current	Structural Biology of Alzheimer's Disease

A. Personal Statement

In my graduate training at UCLA, I was supported by a National Science Foundation Graduate Research Fellowship where I worked in Dr. David Eisenberg's lab to elucidate the mechanisms and pathology of disease-related protein-protein interactions. Dr. Eisenberg is a world-renowned physical biochemist and has an extensive record for training predoctoral and postdoctoral fellows. My technical training extends to multiple structural biology techniques, including traditional X-ray crystallography, and cryo-Electron Microscopy methods such as micro-Electron Diffraction, single particle analysis, and helical reconstruction. To span this range of expertise, I collaborated with other world leaders at UCLA and nationally, including cryo-EM pioneers Dr. Z. Hong Zhou (UCLA), Dr. Tamir Gonen (HHMI Janelia/UCLA), and Dr. Jose Rodriguez (UCLA). Along with my technical training, I trained in scientific communication through regular research presentations at local and international conferences, group research updates and journal clubs. Lastly, my graduate training plan included extensive coursework taught by Dr. Steve Clarke in conducting responsible biomedical research. I am currently a postdoctoral scholar in the lab of Dr. Eisenberg where I am continuing to use cryo-EM to reveal protein-protein interactions that are at the center of human neurodegenerative diseases.

I have been first author or co-author on over 20 publications probing the atomic structures of disease-associated protein-protein interactions, including the first structures of Parkinson's disease-related alpha-synuclein amyloid fibrils with hereditary mutations and ALS-related TDP-43 amyloid fibrils:

1. **Boyer, D. R.*,** Li, B.*, Sun, C., Fan, W., Zhou, K., Hughes, M. P., Sawaya, M. R., Jiang, L.[#] & Eisenberg, D. S.[#] The α-synuclein hereditary mutation E46K unlocks a more stable, pathogenic fibril structure. *PNAS* (2020) doi:10.1073/pnas.1917914117.
2. **Boyer, D. R.*,** Li, B.*, Sun, C., Fan, W., Sawaya, M. R., Jiang, L.[#] & Eisenberg, D. S.[#] Structures of fibrils formed by α-synuclein hereditary disease mutant H50Q reveal new polymorphs. *Nature Structural and Molecular Biology*. 26, 1044–1052 (2019) doi: https://doi.org/10.1038/s41594-019-0322-y.
3. Cao Q*, **Boyer DR***, Ge P, Sawaya, MR, Eisenberg, DS. Cryo-EM structures of Four Polymorphic TDP-43 Amyloid Cores. *Nature Structural and Molecular Biology* (2019).

B. Positions and Honors

Positions and Employment

2012 – 2014	Research Assistant, University of Michigan, Dept. of Chemical Engineering, Ann Arbor, MI
2014	Research Assistant, University of Michigan, Dept. of Chemistry, Ann Arbor, MI
2015	Research and Development Specialist, University of Michigan, Dept. of Chemical Engineering, Ann Arbor, MI
2015	Teaching Assistant (Biochemistry 153L/Biochemistry 153C), University of California, Los Angeles
2018 – 2020	Writing Consultant, Graduate Writing Center, University of California, Los Angeles
2015 – 2021	Graduate Student Research Assistant, Laboratory of Dr. David Eisenberg, University of California, Los Angeles
2021 -	Postdoctoral Scholar, Laboratory of Dr. David Eisenberg, University of California, Los Angeles

Honors

2014	Summer Undergraduate Research Fellowship, University of Michigan
2015 – 2017	Dean's Scholar Award, University of California, Los Angeles
2015 – 2018	University Fellowship, University of California, Los Angeles
2016 – 2017	Cellular and Molecular Biology Training Program, University of California, Los Angeles
2019	FASEB Protein Aggregation Conference NextGen Award
2019	Audree Fowler Award for Protein Science
2017 – 2020	National Science Foundation Graduate Research Fellowship Program
2020	Ralph and Charlene Bauer Research Award
2020 – 2021	Dissertation Year Fellowship
2020 – 2021	Charles E. and Sue K. Young Graduate Student Fellowship Award
2020 – 2021	UC President's Lindau Nobel Laureate Meetings Fellow

C. Contributions to Science

1. Undergraduate Research - Lab of Dr. Lin. In my first project in the lab of Dr. Xiaoxia Lin, I utilized directed evolution to improve isobutanol tolerance in E. coli. This allows the reduction of product inhibition in biofuel-producing E. coli to increase the efficiency of production of the next-generation biofuel isobutanol. I assessed the genotypic and phenotypic changes in *E. coli* strains that were subject to Multiplex Automated Genome Engineering (MAGE) and directed evolution through Multiplex Allele Specific Polymerase Chain Reaction (MASPCR), 96-well-plate growth studies, and MATLAB analysis of bacterial growth. In my second project, I applied a similar method to improve E. coli growth on the waste products of the biofuel production process algal hydrothermal liquefaction. In both projects, we discovered genes involved in E. coli tolerance to external environmental stresses, informing the design of more efficient and environmentally-friendly biofuel production systems.

    a) Nelson MC, Minty JJ, **Boyer DR**, Kistler S, Gao Y, Wang HY, Lin XN. Adaptive evolution and whole-genome sequencing for improvement and understanding of bacterial growth on aqueous co-products of algae hydrothermal liquefaction. *In preparation*.

    b) Nelson MC, Minty JJ, Kistler S, Gao Y, Wang HY, Lin XN, **Boyer DR**., inventors. Compositions and Methods for Generation of Biofuels. *United States US 62/075,609. 2015 November 05*.

2. Undergraduate Research - iGEM. As part of the Michigan Synthetic Biology Team (MSBT), I helped design and characterize a modular antibody single chain variable fragment (scFv) secretion system in E. coli. We discovered that we could fuse the hyperosmotically inducible protein Y (OsmY) to a scFv and express this construct in E. coli. OsmY naturally is secreted into the periplasm and outside of the cell. By attaching the scFv to OsmY, we could not only allow proper folding of the scFv by oxidation of disulfide bonds in the periplasmic compartment, but greatly simplify the downstream purification process by secreting the antibody into the media, thereby obviating cell lysis and separation processes. We presented our findings at one

national conference and the international Genetically Engineered Machine (iGEM) competition as a poster, presentation, and website.

a) Michigan Synthetic Biology Team. Secretion-based Antibody Purification in E. coli. [Internet]. 2014. Available from: http://2014.igem.org/Team:Michigan/Team/.

3. Undergraduate Research - Lab of Dr. Marsh. In the lab of Dr. Neil Marsh, I attempted to identify a novel cofactor necessary for the yeast enzyme Ferulic Acid Decarboxylase. Through a combination of enzymology techniques and mass spectrometry analysis, we demonstrated that this cofactor was shown to be a modified flavin molecule produced by the enzyme Phenylacrylic Acid Decarboxylase 1. This work resulted in one co-authored publication.

   a) Lin F, Ferguson KL, **Boyer DR**, Lin XN, Marsh EN. Isofunctional enzymes PAD1 and UbiX catalyze formation of a novel cofactor required by ferulic acid decarboxylase and 4-hydroxy-3-polyprenylbenzoic acid decarboxylase. *ACS Chem Biol*. 2015 Apr 17;10(4):1137-44. PubMed PMID: 25647642.
   b) **Boyer DR**, Lin F, Ferguson K, Marsh N. Characteristics of Ferulic Acid Decarboxylase (FDC) and Phenylacrylic Acid Decarboxylase 1 (PAD1). Poster. Summer Undergraduate Research Symposium; 2014; Notre Dame, IN, United States.

4. Post-undergraduate Research - Lab of Dr. Nina Lin. I worked as a research specialist after graduating from the University of Michigan in the lab of Dr. Nina Lin in collaboration with her startup company, Ecovia Renewables LLC. I helped to design and characterize synthetic microbial consortia to produce poly-glutamic acid, a biopolymer with properties suitable for both industrial and medical use (e.g., non-immunogenic drug delivery). This work resulted in one provisional patent.

   a) Minty JJ, Singer ME, Lin XN., **Boyer, D.R.** Patent. Compositions and Methods for Microbial Co-culture. *United States US 16/304,336. 2017 May 26*.

5. Graduate Research – Lab of Dr. David Eisenberg. As a graduate student, I elucidated the atomic structures of numerous amyloid proteins associated with different neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Understanding of atomic structures of amyloid proteins facilitates both basic understanding of disease processes as well as structure-based drug design (publication b below). Basic advances to the understanding of amyloid proteins that I have contributed include (i) the effect of hereditary mutations on alpha-synuclein fibril structures (publications #1 and #2 from Personal Statement), (ii) geometrical explanation for the limited width of amyloid fibrils (publication a below), (ii) and ongoing research into the atomic structures of elusive amyloid oligomers (David Boyer PhD Thesis Chapter 6, *under embargo until 2022*).

   a) **Boyer, DR**, Mynhier, NA, Sawaya, MR. Why amyloid fibrils have a limited width. *bioRxiv.* 2021.

   b) Seidler, P.M., **Boyer DR**, Rodriguez, J.A., Sawaya, M.R., Cascio, D., Murray, K.A., Gonen, T., Eisenberg, D.S. Structure-based inhibitors of tau aggregation. *Nature Chemistry* 10, 170–176 (2018).

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: Peng Ge

eRA COMMONS USER NAME (credential, e.g., agency login): gepeng22

POSITION TITLE: Research Specialist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Peking University, Beijing, P.R. China	B.S.	07/01	Chemistry
(matriculated at the age of 14)			
Baylor College of Medicine, Houston, TX	Ph.D.	09/10	Structural Computational Biology and Molecular Biophysics
UCLA, Los Angeles, CA	Post Doc	03/16	Structural Biology

A. Personal Statement

I started my professional training as a structural, organic chemist and a drug designer at Peking University, China. In 2003, I came to the U.S. for my graduate study, first at Rice University in Houston, TX in the area of applied physics and then drifted across the Main Street to Baylor College of Medicine and studied structural biology under the mentorship of several cryoEM structural biologists at the Texas Medical Center. In my 17 years of professional research career, I published a total of 25 papers including 6 articles in top tier journals (3 first author articles) and 13 articles in second tier journals (6 first author articles).

I am well experienced as a structural biologist specialized in cryo-electron microscopy. I believe my contribution will be crucial for the determination of the structural basis of yeast chaperon-prion interaction.

B. Positions and Honors

Professional Experience

2001-2003	Research Assistant, the State Key Laboratory for Structural Chemistry of Unstable and Stable Species, Beijing, China, P.R., supervised by Dr. Luhua Lai
2003-2004	Ph. D. Student, Applied Physics Program, Rice University, Houston, TX 77025
2004-2010	Ph. D. Student, Program in Structure and Computational Biology and Molecular Biophysics, Baylor College of Medicine, Houston, TX 77030
2010-2106	Postdoctoral Scholar, Department of Microbiology, Immunology and Molecular Genetics, UCLA, Los Angeles, CA 90095
2016-2021	Researcher, California Nanosystem Institute, UCLA, Los Angeles, CA 90095
2021-Present	Research Specialist, HHMI, UCLA, Los Angeles, CA 90095

Honors

2003	Dean’s Fellowship, Department of Bioengineering, Rice University, Houston, TX
2006	Keck Viral Imaging Fellowship, Houston, TX
2013	George Palade Award, Microscopy Society of America

2013-15 American Heart Association Western Affiliates Postdoctoral Fellowship
2014 Boyer-Peter Award, Molecular Biology Institute, UCLA, Los Angeles, CA
2015 Chancellor's Award for Postdoctoral Research, UCLA, Los Angeles, CA
2015 Sydney Finegold Award, MIMG Dept, UCLA, Los Angeles, CA

C. Contributions to Science

1. Methodology development for atomic resolution cryoEM.

Very recently, the structural biology method of cryo electron microscopy (cryoEM) has gained public attention as a new way of understanding biological systems. I contributed to the development of cryoEM methods. Publication #d here is the first helical cryoEM structure to reach near atomic resolution. This method is further extended to incorporate the Relion framework that uses maximum-likelihood estimations (#c) and is applied to systems previously too flexible or too fine to study by cryoEM (#a,b).

a. Guenther EL, **Ge P**, Trinh H, Sawaya MR, Cascio D, Boyer DR, Gonen T, Zhou ZH, Eisenberg DS. Atomic-level evidence for packing and positional amyloid polymorphism by segment from TDP-43 RRM2. **Nat Struct Mol Biol.** 25 (2018) 311 PMC6056015

b. Poweleit N, **Ge P**, Nguyen HH, Loo RR, Gunsalus RP, Zhou ZH. CryoEM structure of the Methanospirillum hungatei archaellum reveals structural features distinct from the bacterial flagellum and type IV pilus. **Nat Microbiol**. 2 (2016) 16222 PMC5695567

c. Clemens DL**, **Ge P****, Lee B-Y, Horwitz MA and Zhou ZH Atomic structure and mutagenesis of a type VI secretion system reveals a mesh framework essential to function. **Cell**, 160 (2015) 940-51 PMC4351867 ****Co-First Authors**

d. **Ge P**, Zhou ZH Hydrogen-bonding networks and RNA bases revealed by cryo electron microscopy suggest a triggering mechanism for calcium switches. **Proc Natl Acad Sci USA** 109 (2011) 9637-42 PMC3111329

2. Structural study of Amyloid fibers

Amyloid fibers are central to many neural degenerative diseases such as Frontotemporal lobar degeneration (FTLD, #a-c), mad cow, Alzheimer and Parkinson (#d) diseases. The structural study of these fibers by cryoEM was difficult due to the fine helical parameters. The advent of a direct electron detecting camera provided the required high-resolution contrast at low dose, making possible the determination of many such filaments.

a. Jiang YX, Cao Q, Sawaya MR, Abskharon R, **Ge P**, …, Eisenberg DS. Amyloid fibrils in FTLD-TDP are composed of TMEM106B and not TDP-43. **Nature**. 605(2022) 304

b. Cao Q, Boyer DR, Sawaya MR, **Ge P**, Eisenberg DS. Cryo-EM structures of four polymorphic TDP-43 amyloid cores. **Nat Struct Mol Biol.** 26 (2019) 619 PMC7047951

c. Guenther EL, **Ge P**, Trinh H, Sawaya MR, Cascio D, Boyer DR, Gonen T, Zhou ZH, Eisenberg DS. Atomic-level evidence for packing and positional amyloid polymorphism by segment from TDP-43 RRM2. **Nat Struct Mol Biol.** 25 (2018) 311 PMC6056015

d. Li B**, **Ge P****, Murray KA**, et al. Cryo-EM of full-length α-synuclein reveals fibril polymorphs with a common structural kernel. **Nat Commun.** 9 (2018) 3609 ****Co-First Authors** PMC6127345

3. Structure-function relationship of bacterial contractile nanomachines.

Contractile nanomachines are a collection of bacterial protein assemblies, either intracellular or extracellular, that drive their central tubes into victim cells by force generated with sheath contraction. The atomic resolution structures of these systems provide basis for redesign of such machines (#a,b) and for development of therapeutic agents against such machines (#c).

a. **Ge P****, Scholl D**, Prokhorov NS, Avaylon J, Shneider MM, Browning C, Buth SA, Plattner M, Chakraborty U, Ding K, Leiman PG, Miller JF, Zhou ZH. Action of a minimal contractile bactericidal nanomachine **Nature** 580 (2020) 658-62 ****Co-First Authors** PMC7513463

b. **Ge P**, Scholl D, Leiman PG, Yu X, Miller JF, Zhou ZH Atomic structures of a bactericidal contractile nanotube in its pre- and post-contraction states. **Nat Struct Mol Biol,** 22 (2015) 377-82 PMC4445970

c. Clemens DL**, **Ge P****, Lee B-Y, Horwitz MA and Zhou ZH Atomic structure and mutagenesis of a type VI secretion system reveals a mesh framework essential to function. **Cell**, 160 (2015) 940-51 PMC4351867 ****Co-First Authors**

4. Structural study of RNA viruses

Many human pathogens contain RNA as their genetic material. These include viruses under the families of non-segmented negative-strand RNA viruses (rabies virus, vesicular stomatitis virus and ebola virus, #d), flaviviruses (dengue virus, #b,c) and double strand RNA viruses (bluetongue virus, #a). Atomic structure of these viruses are desirable for the purpose of structure-based drug discovery against these viruses.

a. Kerviel A**, **Ge P****, Lai M**, Jih J, Boyce M, Zhang X, Zhou ZH, Roy P. Atomic structure of the translation regulatory protein NS1 of bluetongue virus. **Nat Microbiol**. 4 (2019) 837-845 PMC6482088

b. **Ge P**, Zhou ZH Class II viral fusion proteins: chaperone, maturation and entropy. **Trends Microbiol.** 22 (2014) 100-106. PMC4445943

c. Zhang X**, **Ge P****, Yu X, Brannan JM, Bi G, Zhang Q, Schein S, Zhou ZH. Cryo-EM structure of the mature dengue virus at 3.5-Å resolution. **Nat Struct Mol Biol.** 20 (2013) 105-110. ****Co-First Authors** (Journal Cover) PMC3593067 (highly cited article)

d. **Ge P**, Tsao J, Schein S, Green TJ, Luo M, Zhou ZH. Cryo-EM model of the bullet-shaped vesicular stomatitis virus. **Science** 327 (2010) 689-93. PMC2892700

5. Structural study of single particle protein complexes

a. Jiang J, Magilnick N, Tsirulnikov K, Abuladze N, Atanasov I, **Ge P**, Narla M, Pushkin A, Zhou ZH, Kurtz I. Single particle electron microscopy analysis of the bovine anion exchanger 1 reveals a flexible linker connecting the cytoplasmic and membrane domains. **Plos One**. 8 (2013) e55408. PMC3564912

b. Huang CS, **Ge P**, Zhou ZH, Tong L An unanticipated architecture of the 750-kDa $\alpha_6\beta_6$ holoenzyme of 3-methylcrotonyl-CoA carboxylase. **Nature** 481 (2012) 219-223. PMC3271731

c. Green TJ, Rowse M, Tsao J, Kang J, **Ge P**, Zhou ZH and Luo M Access of RNA encapsidated in the nucleocapsid of vesicular stomatitis virus, **J. Virol.** 85 (2011) 2714-2722. PMC3067934

d. Li F, **Ge P**, Hui WH, Atanasov I, Rogers K, Guo Q, Osato D, Falick AM, Zhou ZH, Simpson L Structure of the core editing complex (L-complex) involved in uridine insertion/deletion RNA editing in trypanosomatid mitochondria. **Proc Natl Acad Sci USA** 106 (2009) 12306-10 PMC2708173

Complete List of Published Work:
https://www.ncbi.nlm.nih.gov/myncbi/peng.ge.1/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

None

Completed Research Support

13POST17340020 Peng Ge (Awardee) Z. Hong Zhou (Advisor) 07/01/2013 – 06/30/2015
American Heart Association Western Affiliates Postdoctoral Fellowship

Atomic Structures of Actin and Actomyocin
The propose of the research is to solve the structure of actin and actomyocin by cryoelectron microscopy to ~3 Å resolution
Role: Trainee

OMB No. 0925-0001 and 0925-0002 (Rev. 03/2020 Approved Through 02/28/2023)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Abskharon, Romany

eRA COMMONS USER NAME (credential, e.g., agency login): ROMANY_ABSKHARON

POSITION TITLE: Project Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	START DATE MM/YYYY	END DATE MM/YYYY	FIELD OF STUDY
College of Science, Assiut Unvi., Egypt	B.Sc.	09/1999	06/2002	Chemistry & Microbiology
College of Science, Assiut Unvi., Egypt	M.Sc.	09/2004	02/2008	Chemistry & Microbiology
Vrije Universiteit Brussels, Belgium (VIB Research Institute)	Ph.D.	03/2008	06/2013	Immunology & Structure Biology
National Institute of Oceanography & Fisheries, Cairo, Egypt	Lecturer	06/2013	08/2014	Bio-engineering Science
Van Andel Research Institute, Grand Rapids, MI, USA	Postdoctoral Researcher	09/2014	12/2017	Protein-misfolding in neurodegenerative disease
University of California, Los Angeles, USA	Postdoctoral Researcher	01/2018	09/2020	Structure-based design to understand and treat neurodegenerative disease
University of California, Los Angeles, USA	Project Scientist	09/2020	Present	Structure-based design to understand and treat neurodegenerative disease

A. Personal Statement

My overall goal as a scientist is to use structure-based design, structure biology and immunological approaches to understand and treat neurodegenerative diseases. During my career, I published 25 papers, and currently have three under preparation. As graduate student under the supervision of **Prof. Jan Steyaert**, I solved the first crystal structure of full-length human prion protein in complex with a nanobody. In this project, I had successes in generating, selecting and characterizing a number of nanobodies against prion proteins. I have also developed an innovative expression system for production of soluble prion proteins in *E. coli*. During my first postdoctoral-experience at Center for Neurodegenerative Science (Van Andel Research Institute), I focused on studying nanobodies as potential therapeutic approaches for protein misfolding-induced neurodegenerative diseases, such as Parkinson's disease and prion disease.

In 2018, I was honored to join **Prof. David Eisenberg's lab,** and as a senior postdoctoral researcher, my goal is to use structure-based design and structure biology to further understand and treat neurodegenerative

diseases. I initiated four projects: **In the first project**, I designed and engineered a single-chain antibody (scFv-M204), that inhibits seeding by tau oligomers and pathological extracts from donors with Alzheimer's disease (AD) and Chronic Traumatic Encephalopathy (CTE). Remarkably, the scFv-M204 antibody binds to oligomeric tau, but not to recombinant monomers or fibrils (a patent has been accepted and a paper has been published in JBC). Additionally, I expressed and purified several monoclonal antibodies that specifically bind to certain regions of tau protein from hybridoma cell lines. **In my second project**, I used cryo-EM in determining the structures of full-length fibrils of tau protein both seeded by fibrils purified from autopsied Alzheimer's disease (AD) brains and by unseeded fibrils. In both samples, tau fibrils are generated using a new method in which RNA is used as a natural co-factor for aggregation (One paper has been published in PNAS and second manuscript in preparation). **In the third project**, I employed the structure-based approach to design a panel of synthetic nanobody inhibitors to block the prion-like spread by extracts from autopsied brains of patients with AD and progressive supranuclear palsy (PSP) (a patent and manuscript are in preparation). **In the fourth project**, Determine the structure of recombinant tau oligomers and AD brain extracted oligomers in complex with antibody fragments (Fabs and nanobodies). Since 2018, my collaborations with various Eisenberg lab members have led to five manuscripts as first author (two published and three under preparation as first author) and many other papers under revision as co-author.

a) **Abskharon R.**, Sawaya MR., Boyer DR., Cao Q, Nguyen BA., Cascio D., Eisenberg DS (2022). Cryo-EM structure of RNA-induced tau fibrils reveals a small C-terminal core that may nucleate fibril formation. PNAS. 119(15):e2119952119. PMID: 35377792.

b) Jiang YX., Cao Qin., Sawaya MR., **Abskharon R**., Ge P., DeTure M., Dickson D., Fu J., Loo R., Loo J., Eisenberg D.S. (2022). Amyloid fibrils in disease FTLD-TDP are composed of TMEM106B not TDP-43. Nature. 605(7909):304-309. PMID: 35344984.
Cao Q., Boyer DR., Sawaya MR., **Abskharon R**., Saelices L., Nguyen BA., Lu J., Kandee F., Eisenberg DS., (2021). Cryo-EM structures of hIAPP fibrils seeded by patient-extracted fibrils reveal new polymorphs and conserved fibril cores. Nat Struct Mol Biol. 28(9):724-730. PMID: 34518699.

c) **Abskharon R**., Seidler PM., Sawaya MR., Cascio D., Yang P., Philipp S., Williams CK., Newell KL., Ghetti B, DeTure MA., Dickson DW., Vinters HV., Felgner PL., Nakajima R., Glabe CG., Eisenberg DS (2020). Crystal structure of a conformational antibody that binds tau oligomers and inhibits pathological seeding by extracts from donors with Alzheimer's disease. J. Biol. Chem. 295:10662-10676. PMCID: PMC7397112.

B. Positions and Honors

Positions and Employment

2004 -2008	Researcher assistant, College of Science, Assiut University, Egypt.
2008 - 2013	PhD student, Vrije Universiteit Brussels, Brussels, Belgium (Supervisor: Dr. Jan Steyaert).
2013 - 2014	Lecturer, National Institute of Oceanography & Fisheries, Cairo, Egypt.
2014 - 2017	Postdoctoral Fellow, Van Andel Research Institute, Grand Rapids, MI, USA.
2018 - 2020	Postdoctoral Fellow, University of California, Los Angeles (Supervisor: Dr. David Eisenberg).
2020 - Present	Project Scientist, University of California, Los Angeles (Supervisor: Dr. David Eisenberg).

Honors

2011	RAMC Award for the best poster presentation from RAMC (Recent Advances in Macromolecular Crystallization) Strasbourg, France.
2012	HERCULES Award for the best poster presentation from the School of Neutrons & Synchrotron Radiation for Science, Grenoble, France.
2012	Prion Award, for the best poster presentation from NeuroPrion committee at the international annual Prion conference, Amsterdam, Netherland.
2016	APSPR Award, Asia Pacific Society of Prion Research (APSPR) travel Award, Tokyo, Japan.
2019	State Encouragement Awards in Biological Science, from Egyptian Academy of Scientific Research and Technology.
2020	Scientific Creativity and Innovation "Makram Mehanna" Award, from the Coptic Orthodox Cultural Center.
2020	First class Medal of Science and Arts, from Arab Republic of Egypt (from the president of Egypt).

Other Experience and Professional Memberships

2010 NATO ASI, 10th Course: Biophysics and Structure. Organized by Stanford School of Medicine in Ettore Majorana Center for Scientific Culture in Erice, Sicily (EMFCSC), Italy.

2010 The BCA/CCP4 Protein Crystallography Summer School. Organized by British crystallographic community in Oxford University Diamond Light Source, UK.

2012 HERCULES European School of Crystallography: One-month course, coordinated by the Université Grenoble, EMBL, and ESRF, at European Synchrotron Radiation Facility (Grenoble, France), Swiss Light Source / Paul Scherrer Institute in Villigen, Switzerland and SOLEIL (St Aubin, France).

2016 Member of Asia Pacific Society of Prion Research (APSPR).

2019 Member of Antibody Society.

2019 Member of Alzheimer's Association.

C. Contribution to Science

1. Graduate Career:

The focus of my dissertation work was on the structural investigation of prion proteins using nanobody-aided crystallography. I determined the first structure of full-length prion protein in complex with a nanobody. Nanobodies are single domain antibodies derived from Camelidae. These nanobodies stabilize particular conformers of prions, making this aggregating protein amenable to X-ray crystallography. I have had successes in generating, selecting and characterizing a large number of nanobodies against prion proteins**.** I also developed an innovative expression system for production of soluble prion proteins in *E. coli*. Prior to my work, production of recombinant PrP was only achieved by refolding protocols. I discovered that the co-expression of two different PrP^{C} (normal form of prion) with the human Quiescin Sulfhydryl OXidase (QSOX), a human chaperone with thiol/disulfide oxidase activity, in the cytoplasm of *E. coli* produces soluble recombinant PrP. Furthermore, I discovered that QSOX inhibits human prion propagation in the cell-free protein misfolding cyclic amplification and inhibits murine prion propagation in scrape-infected neuroblastoma cells. I also determined QSOX preferentially binds PrP^{Sc} from prion-infected human or animal brains but not PrP^{C} from uninfected brains. My finding provides a useful tool for prion diagnosis. My study indicates that QSOX plays a role in prion formation, which opens new venues for developing therapeutic targets in prion or other neurodegenerative diseases. Indeed, I successfully utilized nanobody-assisted X-ray crystallography to solve the very first structures of the full-length human prion protein (PrP) and its C-terminal truncated version and solved the structure at 1.5 Å resolutions. The new structure provides the first structural elements leading to the disease-causing conversion. To determine whether this critical epitope is important to preventing and/or treating prion diseases, I used nanobody-assisted crystallography, a power tool to unveil local structural features of intrinsically disordered proteins. My solved structure supports the notion that the conserved palindromic sequence mediates β-enrichment in the PrP^{C} monomer as one of the early events in prion formation. I discovered that Nb484 is a unique crystallization chaperone for mouse prion (1.2 Å) and other pathological human mutants such as. V210I (1.5 Å) and E219K (1.5 Å).

Research Papers:

a) **Abskharon R**., Giachin G., Wohlkonig A., Soror S.H., Pardon E., Legname G., Steyaert J. (2014). Probing the N-Terminal β-Sheet Conversion in The Human Prion Protein Bound To A Nanobody, Journal of the American Chemical Society, 136; 3: 937-944.

b) Yuan J.*, Zhan A.Y.*, **Abskharon R***., Xiao X., Martinez M.C., Knealeg G., Jacqueline M., Lehmann S., Castillaj J., Steyaert J., Kong Q., Petersen R.B., Wohlkonig A., Zou W.Q. (2013). Recombinant Human Prion Protein Inhibits Prion Propagation in vitro, Scientific Reports- Nature Publishing group, 9; 3: 2911. PMCID: PMC3793212. ***Co-first author.**

c) **Abskharon R**., Ramboarin S., Hassan H.E., Gad W., Apostol M.I., Giachin G., Legname G., Steyaert J., Messens J., Soror S.H., Wohlkonig A. (2012). A novel expression system for production of soluble prion proteins in E. coli, Microbial Cell Factories, 10; 11:6. PMCID: PMC3283519. **Flagged highly accessed paper on Biomed central.**

d) **Abskharon R**., Soror S.H., Pardon E., Hassan H.E., Legname G., Steyaert J., Wohlkonig A. (2011). Combining in situ proteolysis and microseed matrix screening to promote crystallization of PrPC-nanobody complexes, Protein Engineering, Design, and Selection, 24;9: 737-41.

2. First Postdoctoral Career:

I focused on generating nanobodies as therapeutic approaches for protein-misfolding induced neurodegenerative diseases, such as Parkinson's disease and prion disease. I used a prion disease model to investigate the therapeutic values of nanobodies generated against PrP^{Sc}, the misfolded prion protein (PrP) that causes prion diseases. I have screened and characterized 35 nanobodies against different PrP confomers, including the normal prion protein (PrP^{C}), the misfolded PrP intermediate (PrPI) and the misfolded diseased causing PrP^{Sc}. While most of the nanobodies have high binding affinity for the normal prion protein (PrP^{C}), some are able to discriminate between the misfolded (PrPI and PrP^{Sc}) and normal (PrP^{C}) form. Interestingly, one of the nanobodies, Nb196, binds strongly to a misfolded neurotoxic PrP species, cytosolic PrP, both *in vitro* in test tubes and *ex vivo* in cultured cells and able to decrease the prion infectivity by 99%. Our data suggested that Nanobodies can assist in investigating the structural mechanism that governs the PrP misfolding. I also established two Nanobodies libraries by immunizing alpaca with various amyloid fibrils of prion and A-syn proteins.

Research Papers:

a) Wang F, Wang X, **Abskharon** R, Ma J. (2018). Prion infectivity is encoded exclusively within the structure of proteinase K-resistant fragments of synthetically generated recombinant PrPSc. Acta Neuropathol Commun. 24,6(1):30. PMCID: PMC5921397.

b) **Abskharon R**., Dang J., Elfarash A., Wang Z., Shen P., Zou S.L., Hassan S., Wang F., Fujioka H., Steyaert J., Mulaj M., Surewicz K. W, Castilla J., Wohlkonig A., Zou W.Q. (2017). Soluble polymorphic bank vole prion proteins induced by co-expression of quiescin sulfhydryl oxidase in E. coli and their aggregation behaviors. Microbial Cell Factories. 16:170. PMCID: PMC5628483.

c) Zhan A.Y*., **Abskharon R***., Yuan J., Martinez C.M., Xiao X., Jacquelin M., Lehmann S., Steyaert J., Kong Q., Petersen B.R., Wohlkonig A., Zou W.Q. (2016). Quiescin-sulfhydryloxidase inhibits prion formation in vitro, Aging (Albany NY), 8, 12: 3419–3429. PMCID: PMC5270677. ***Co-first author**

d) **Abskharon R**., Wang F., Vander Stel J.K., Sinniah K., Ma J. (2016). The role of the unusual threonine string in the conversion of prion protein, Scientific Reports- Nature Publishing Group, 6, 38877. PMCID: PMC5159806.

3. Second Postdoctoral Career: I joined **Dr. David Eisenberg's** laboratory in 2018 as a senior postdoctoral fellow with the aims of **a)** Using structure-based design to develop synthetic nanobody inhibitors of pathological tau aggregation, and **b)** Determine the high-resolution molecular structures of tau oligomers using tau-specific antibodies. For this project, I developed an expression system to produce a single chain antibody (scFv) in bacteria that specifically binds to tau oligomers. Furthermore, this antibody shows a potential effect for inhibiting tau aggregation and seeding by AD brain patients' samples. Additionally, I established the expression and the purification of several monoclonal antibodies that specifically bind to certain regions of Tau protein from hybridoma cell lines. When I joined the **Eisenberg laboratory**, I had the opportunity to work with many exceptional scientists in structure-based design field. This allowed me to design a panel of *de novo* nanobody inhibitors for tau seeding by extracts from autopsied brains of patients with Alzhimer's disease and other tauopathies.

Research Papers:

a) **Abskharon R.**, Sawaya MR., Boyer DR., Cao Q, Nguyen BA., Cascio D., Eisenberg DS (2022). Cryo-EM structure of RNA-induced tau fibrils reveals a small C-terminal core that may nucleate fibril formation. PNAS. 119(15):e2119952119. PMID: 35377792.

b) Jiang YX., Cao Qin., Sawaya MR., **Abskharon R**., Ge P., DeTure M., Dickson D., Fu J., Loo R., Loo J., Eisenberg D.S. (2022). Amyloid fibrils in disease FTLD-TDP are composed of TMEM106B not TDP-43. Nature. 605(7909):304-309. PMID: 35344984.

c) Cao Q., Boyer DR., Sawaya MR., **Abskharon R**., Saelices L., Nguyen BA., Lu J., Kandee F., Eisenberg DS., (2021). Cryo-EM structures of hIAPP fibrils seeded by patient-extracted fibrils reveal new polymorphs and conserved fibril cores. Nat Struct Mol Biol. 28(9):724-730. PMID: 34518699.

d) **Abskharon R**., Seidler PM., Sawaya MR., Cascio D., Yang P., Philipp S., Williams CK., Newell KL., Ghetti B, DeTure MA., Dickson DW., Vinters HV., Felgner PL., Nakajima R., Glabe CG., Eisenberg DS (2020). Crystal structure of a conformational antibody that binds tau oligomers and inhibits pathological seeding by extracts from donors with Alzheimer's disease. J. Biol. Chem. 295:10662-10676. PMCID: PMC7397112.

4. Other publications from my undergraduate carrier in Egypt

a) Hassan SH., Van Ginkel S., Hussein M., **Abskharon R**., Oh S. (2016). Toxicity assessment using different bioassays and microbial biosensors. Environment International, 92, 106–118.

b) **Abskharon R**., Hassan S., Kabir M.H., Qadir S.A., Gad El-Rab S., Wang M.H. (2009). The Role of Antioxidants Enzymes of E. coli ASU3, a Tolerant Strain to Heavy Metals Toxicity, in combating oxidative stress. World Journal of Microbiology and Biotechnology, 26; 2: 241-247. DOI: 10.1007/s11274-009-0166-4.

c) Hassan S.H., **Abskharon R**., Gad-Elrab S., Ahmed Shoreit A. (2008). Characterization of heavy metal resistant strain Pseudomonas aeruginosa isolated from polluted sites in Assiut, Egypt, Journal of Basic Microbiology, 48; 168–176.

d) **Abskharon R**, Hassan SH, Gad-Elrab SM, Shoreit A (2008). Heavy metal resistant of E. coli isolated from wastewater sites in Assiut city, Egypt. Bulletin of Environmental Contamination and Toxicology 81; 309–315.

Complete List of Published Work in My Bibliography
https://pubmed.ncbi.nlm.nih.gov/?term=Abskharon&sort=date

Selected Conferences:

1. **Poster presentation:** Atomic structures of a single chain antibody that binds and inhibits seeding by tau oligomers. Antibody engineering and therapeutics conference 2019 take place at Marriott Marquis San Diego, California, December 9th - ,13th 2019.
2. **Poster presentation**: Atomic structures of a single chain antibody that binds and inhibits seeding by tau oligomers. Advances in Protein Science – Structure & Function, Engineering & Design A scientific conference, hosted by Amgen in 1050 Rancho Conejo Blvd Thousand Oaks, CA 91320, 10th August 2018.
3. **Poster presentation:** The influence of Prnpb polymorphisms and the conserved 4-threonine stretch of alpha-helix 2 on prion protein conversion, Tokyo, Japan. May 2016.
4. **Poster presentation:** Aglycosylated recombinant prion protein inhibits prion propagation in vitro. PRION 2013, in Banff, Alberta, Canada from May 2013.
5. **Poster presentation**: Quiescin-sulfhydryl oxidase inhibits prion formation in vitro. PRION 2013, in Banff, Alberta, Canada from May 2013.
6. **Oral presentation:** Crystal Structure of a full-length Human PrP/Nanobody complex. Prion, 2012, Amsterdam, Netherlands.

NEWS:

Nature NEWS AND VIEWS, An unexpected protein aggregate in diseased and ageing brains: https://www.nature.com/articles/d41586-022-00873-2.

Science, Frontotemporal Dementia: Not the Protein We Thought. https://www.science.org/content/blog-post/frontotemporal-dementia-not-protein-we-thought

ScienceDaily, The shape of infectious prions: *https://www.sciencedaily.com/releases/2014./01/140124082602.htm*.

ScienceDaily, Recombinant human prion protein inhibits prion propagation: *https://www.sciencedaily.com/releases/2013/10/131009125743.htm*.

ScienceDaily, Two studies describe the function of PrP^{C}, the 'good' alter ego of prions: *https://www.sciencedaily.com/releases/2016/10/161017083931.htm*.

The European Synchrotron Radiation Facility (ESRF), Shaping the early event of prion formation: *http://www.esrf.eu/home/UsersAndScience/Publications/Highlights/highlights-2014/SB/SB13.html.*

The Latest Science, Recombinant human prion protein inhibits prion propagation: *http://www.thelatestscience.com/biology/neuroscience.php?pageNum_nsrs1=45&totalRows_nsrs1=919*

D. Additional Information: Research Support and/or Scholastic Performance

Current Research support: None

Completed Research Support: None

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: Jiang, Yi Xiao

eRA COMMONS USER NAME (credential, e.g., agency login): YIXIAOJIANG

POSITION TITLE: Ph.D. Candidate

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
McGill University, Montréal, Canada	B.S.	06/2018	Biochemistry
University of California, Los Angeles, Los Angeles, California	Ph.D.	In progress	Molecular Biology

A. Personal Statement

In my early research career, I've been fascinated by structural biology and its potential to help us learn about protein function in health and dysregulation in disease. For my undergraduate honours thesis with Dr. T. Martin Schmeing at McGill University, I studied microbial mega-enzyme complexes called polyketide synthases (PKSs), which synthesize valuable biomolecules from simple substrates. Using a combination of x-ray crystallography and organic chemistry, I investigated the mechanisms of substrate selection by the gatekeeping thioesterase domain. Currently in my graduate studies with Dr. David Eisenberg at UCLA, I am applying cryo-EM to study proteins associated with amyloid disorders. I extracted amyloid fibrils from brains of patients with frontotemporal lobar degeneration (FTLD) and imaged these particles using cryo-EM. Structural determination enabled us to visualize the prion-like protein assemblies derived from disease tissues, and introduced a new amyloid protein to the field of neurodegeneration: TMEM106B. I am also excited about translating the information learned from atomic-level structures of pathological protein aggregates into the design of structure-based therapeutics.

Dr. Eisenberg is a world-renowned physical biochemist and has an extensive record of mentoring predoctoral and postdoctoral scientists who continue onto prolific careers in academic and industry research. My technical training focuses on computational and structural biology, which I can apply to fundamental questions in biology. I have a passion for teaching; I actively mentor undergraduate and graduate students in the lab and have served as a teaching assistant in UCLA undergraduate courses. In addition to my research, I am honing my skills in science communication by presenting at group meetings, conferences, and outreach programs.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2016 Research Assistant, Rosalind & Morris Goodman Cancer Research Center, Montréal, Canada

Other Experiences and Professional Memberships

2015-2017 Council Executive, McGill Biochemistry Undergraduate Society
2017-2018 President, McGill Biochemistry Undergraduate Society
2019-present Member, UCLA Science Policy Group

Honors

2015 Keyfitz Scholar, McGill University

2017 Undergraduate Student Research Award, The Natural Sciences and Engineering Research Council
2017 NSERC Bursary Supplement, Fonds de Recherche du Québec Nature et Technologies
2018 First Class Honours in Biochemistry, McGill University
2021 Whitcome Pre-Doctoral Fellowship in Molecular Biology, UCLA
2022 Travel Award, Biophysical Society
2022 Audree V. Fowler Fellowship in Protein Science, UCLA
2022 Life Science Dean's Excellence Award, UCLA

C. Contribution to Science

1) **Discovery of a new amyloid protein in dementia patient brains.** We extracted amyloid fibrils from post-mortem brains of four frontotemporal lobar degeneration (FTLD) patients. Cryo-EM study of these samples revealed that fibrils are made up of transmembrane protein 106B (TMEM106B), a protein previously not known to aggregate *in vitro* or in disease. Identification of TMEM106B raises questions about its mechanism of aggregation and pathogenic involvement, answers to which may guide interventional strategies for FTLD.

   a) **Jiang, Y.†,** Cao, Q.†, Sawaya, M.R., Abskharon, R., Ge, P., DeTure, M., Dickson, D.W., Fu, J.Y., Ogorzalek Loo, R.R., Loo, J.A., Eisenberg, D.S. Amyloid fibrils in disease FTLD-TDP are composed of TMEM106B not TDP-43. *Nature* 605, 304–309 (2022). DOI: **https://10.1038/s41586-022-04670-9**. PMID: 35344984.

2) **Structure-based design of inhibitors of amyloid aggregation.** We determined crystallographic structures of amyloid-forming segments from SARS-CoV-2 nucleocapsid protein. I used these "steric-zipper" structures to guide the design of aggregation inhibitors, as potential disruptors of viral replication.

   a) Tayeb-Fligelman, E., Cheng, X., Tai, C., Bowler, J.T., Griner, S., Sawaya, M.R., Seidler, P.M., **Jiang, Y.,** Lu, J., Rosenberg, G.M., Salwinski, L., Abskharon, R., Zee, C., Hou, K., Li, Y., Boyer, D.R., Murray, K.A., Falcon, G., Anderson, D.H., Cascio, D., Saelices, L., Damoiseaux, R., Guo, F., Eisenberg, D.S. Inhibition of amyloid formation of the Nucleoprotein of SARS-CoV-2. *BioRxiv* (2021). DOI: https://doi.org/10.1101/2021.03.05.434000**.**

D. Additional Information: Research Support and/or Scholastic Performance

Scholastic Performance

YEAR	COURSE TITLE	GRADE
	MCGILL UNIVERSITY	
2015	Molecular Biology	B
2015	Introduction to Organic Chemistry I	A
2015	Calculus II	A
2015	Introduction to Physics – Mechanics	A
2016	Molecular Mechanisms of Cell Function	A-
2016	Laboratory Methods in Biochemistry and Molecular Biology I	A
2016	Physical Chemistry in Biological Science I	B-
2016	Introduction to Organic Chemistry II	A-
2016	Introduction to Physics – Electromagnetism	A
2016	Foundations of Programming	A
2016	Metabolic Biochemistry	A
2016	Laboratory Methods in Biochemistry and Molecular Biology II	A-
2016	Introduction to Organic Chemistry III	A-
2016	Principles of Statistics I	A

YEAR	COURSE TITLE	GRADE
2016	Mammalian Physiology	A
2017	Introduction to Molecular and Cell Biology	A-
2017	Biochemistry of Macromolecules	B+
2017	Undergraduate Research Project	A
2017	Basic Genetics	A
2017	Advanced Organic Chemistry Laboratory	A
2017	Protein Structure and Function	A-
2017	Nucleic Acids	B+
2017	Research Laboratory in Biochemistry	A
2017	International Migration	A
2018	Science of Storms	A-
2018	Biophysical Methods in Biochemistry	B+
2018	Independent Research	A
2018	Physical Chemistry in Biological Science II	A
	UNIVERSITY OF CALIFORNIA, LOS ANGELES	
2018	Structure, Function and Dynamics of Macromolecular Assemblies	B
2018	Mitochondria, Proteostasis and Neurodegenerative Diseases	A-
2019	Structural Molecular Biology	A-
2019	Structural Molecular Biology Laboratory	A
2019	Scientific Writing	A
2019	Proteomics and Protein Mass Spectrometry	A
2020	Applied Bioinformatics Laboratory for Biologists	A+