BIOGRAPHICAL SKETCH

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NAME: Lee, Myungwoon

eRA COMMONS USER NAME (credential, e.g., agency login): leemw1

POSITION TITLE: Assistant Professor

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)	END DATE MM/YYYY	FIELD OF STUDY
University of Seoul, Seoul	BS	02/2006	Physics
Massachusetts Institute of Technology, Cambridge, MA	PHD	08/2018	Physical Chemistry
National Institutes of Health, Bethesda, MD	Postdoctoral Fellow	11/2022	Physical Chemistry

A. Personal Statement

My research aims to provide structural and mechanistic basis of misfolded protein aggregation that cause neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. During my Ph.D., I investigated the molecular interactions between membranes and viral fusion proteins using solid-state NMR spectroscopy (ssNMR), focusing on how these interactions enable proteins to adopt functional conformations. Building on this foundation, my postdoctoral research shifted toward characterizing the molecular structures of amyloid fibrils and understanding the interactions that drive and stabilize their aggregation neurodegenerative contexts by employing ssNMR and cryo-electron microscopy (cryo-EM).

Leveraging my expertise in biophysical chemistry, particularly ssNMR and cryo-EM, my current research focuses on elucidating how specific molecular interactions regulate protein aggregation, drive structural polymorphisms of amyloid fibrils, and contribute to their conformation-dependent pathologies. Recent studies from my group have shown that α-synuclein exhibits membrane-dependent structural polymorphism and misfolding pathways. We observed that distinct fibril conformations display different membrane-association, implying that specific lipid-protein interactions regulate both protein aggregation and fibril structure. To further probe structure-pathology relationships, we are employing brain-on-a-chip models to examine conformation-specific neuronal dysfunctions and to better understand the structural determinants of neurodegeneration by collaborating with Dr. Jungwook Paek in Binghamton University.

Ongoing Projects List

R21 NS139178. (PI), 09/01/2024 – 08/31/2026

Investigating the interplay between polymorphic α-syn fibril conformation and cell-dependent pathology.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2023 -	Assistant Professor, Department of Chemistry, Drexel University, Philadelphia, PA
2021 - 2022	Member of Biophysical Society, Biophysical Society
2021 - 2022	Intramural Research Training Associate, National Institutes of Health, Bethesda, MD
2018 - 2021	Visiting Fellow, National Institutes of Health, Bethesda, MD
2014 - 2018	Graduate Research Assistant, Massachusetts Institute of Technology, Cambridge, MA
2012 - 2014	Graduate Research Assistant, Iowa State University, Ames, IA
2006 - 2010	Senior Engineer, Samsung Electronics Corporations

Honors

2023	The protein aggregation conference Travel Award, Federation of American Societies for Experimental Biology

2005 Financial Aid Scholarship-The 2nd Term of 2005, University of Seoul
2005 Scholarship for Excellent Achievement-The 1st Term of 2005, University of Seoul
2004 Scholarship for Excellent Achievement-The 1st Term of 2004, University of Seoul
2003 Financial Aid Scholarship-The 1st Term of 2003, University of Seoul

C. Contribution to Science

1. Molecular structures and interactions of neurodegenerative protein aggregations.

   A wide range of neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), is associated with abnormal protein aggregation from their normal soluble forms to amyloid fibrils, filament-like protein structures composed of the β-sheet fold. Therefore, understanding the molecular structures of these protein aggregations and the interactions stabilizing amyloid fibril formation will contribute to the development of amyloid-forming inhibitors, potentially leading to effective therapies for these tragic diseases, which currently lack a cure. Thus far, by combining solid-state NMR (ssNMR) and cryo-electron microscopy (cryo-EM), I have developed a high-resolution molecular structural model for fibrils formed by the C-terminal low complexity domain of the RNA binding protein fused in sarcoma (FUS), which is known to be associated with ALS and frontotemporal dementia (FTD). The precise and unambiguous structure of the C-terminal FUS fibrils permits detailed characterization of stabilizing interactions within the fibril core, providing new insights into protein-protein interactions underlying non-hydrophobic amyloid fibril formation. Another main thrust of my research is to explore the polymorphisms of amyloid fibrils that have been proposed to correlate with variations in disease phenotypes. Thus, I examined the molecular structure of the Aβ42 fibrils derived from the brain tissue of the typical AD patient through seeded growth. Our study reports two predominant polymorphs that differ from the previously reported structures, exhibiting distinct molecular stabilizing interactions. These results expand our understanding of Aβ42 amyloid polymorphisms that may have implications for the design of aggregation inhibitors and amyloid imaging agents based on structural specificities. The proposed research will elucidate the intricate interplay among amyloid-forming proteins during neurodegenerative fibril formation and their role in determining fibril structures and associated pathological effects.

   a. Wilson CB, Lee M, Yau WM, Tycko R. Conformations of a low-complexity protein in homogeneous and phase-separated frozen solutions. Biophys J. 2024 Dec 3;123(23):4097-4114. PubMed Central PMCID: PMC11628836.
   b. Lee M, Yau WM, Louis JM, Tycko R. Structures of brain-derived 42-residue amyloid-β fibril polymorphs with unusual molecular conformations and intermolecular interactions. Proc Natl Acad Sci U S A. 2023 Mar 14;120(11):e2218831120. PubMed Central PMCID: PMC10089215.
   c. Lee M, Ghosh U, Thurber KR, Kato M, Tycko R. Molecular structure and interactions within amyloid-like fibrils formed by a low-complexity protein sequence from FUS. Nat Commun. 2020 Nov 12;11(1):5735. PubMed Central PMCID: PMC7665218.
   d. Lee M, Wang T, Makhlynets OV, Wu Y, Polizzi NF, Wu H, Gosavi PM, Stöhr J, Korendovych IV, DeGrado WF, Hong M. Zinc-binding structure of a catalytic amyloid from solid-state NMR. Proc Natl Acad Sci U S A. 2017 Jun 13;114(24):6191-6196. PubMed Central PMCID: PMC5474797.

2. Structures and lipid interactions of viral fusion proteins.

   Enveloped viruses, including human pathogens such as human immunodeficiency virus (HIV), Ebola virus, and parainfluenza viruses (PIV), rely on virus−cell membrane fusion to enter target cells and initiate the virus replication. Although this fusion process involves conformational changes in the viral fusion proteins to trigger the membrane dehydration and membrane structural changes from the lamellar state to the final fusion state, little is known about key hydrophobic domains of the fusion protein, the N-terminal fusion peptide (FP) and the C-terminal transmembrane domain (TMD), which play essential roles in destabilizing the host cell and viral membranes. In this context, I employed ssNMR to investigate the structure and lipid interactions of the FP and TMD of viral fusion proteins bound in biologically relevant lipid membranes. The studies of the PIV fusion protein indicate that membrane-dependent conformational changes of both FP and TMD are responsible for generating membrane curvature and transient dehydration. Furthermore, I determined the molecular structure of the C-terminal membrane-interacting region of the HIV fusion protein gp41, housing

the membrane-proximal external region (MPER). This region contains epitopes for four neutralizing antibodies and is connected to the TMD that stabilizes the protein in the virus lipid envelope. I discovered that MPER-TMD exists as a trimeric helix-turn-helix structure in the native environment of cholesterol-containing phospholipid bilayers. These results point to the role of the surface-bound MPER helix in interactions with the N-terminal fusion peptide proximal region (FPPR) of gp41 during viral fusion, completing the membrane fusion process. Subsequent studies focusing on the full length of gp41 confirm the presence of strong interactions between the MPER and FPPR near the membrane surface, providing further guidance on the exact mechanistic role of the domain in virus entry into host cells.

a. Lee M, Morgan CA, Hong M. Fully hydrophobic HIV gp41 adopts a hemifusion-like conformation in phospholipid bilayers. J Biol Chem. 2019 Oct 4;294(40):14732-14744. PubMed Central PMCID: PMC6779440.
b. Kwon B, Lee M, Waring AJ, Hong M. Oligomeric Structure and Three-Dimensional Fold of the HIV gp41 Membrane-Proximal External Region and Transmembrane Domain in Phospholipid Bilayers. J Am Chem Soc. 2018 Jul 5;140(26):8246-8259. PubMed Central PMCID: PMC6382510.
c. Lee M, Yao H, Kwon B, Waring AJ, Ruchala P, Singh C, Hong M. Conformation and Trimer Association of the Transmembrane Domain of the Parainfluenza Virus Fusion Protein in Lipid Bilayers from Solid-State NMR: Insights into the Sequence Determinants of Trimer Structure and Fusion Activity. J Mol Biol. 2018 Mar 2;430(5):695-709. PubMed Central PMCID: PMC5831503.
d. Yao H, Lee M, Liao SY, Hong M. Solid-State Nuclear Magnetic Resonance Investigation of the Structural Topology and Lipid Interactions of a Viral Fusion Protein Chimera Containing the Fusion Peptide and Transmembrane Domain. Biochemistry. 2016 Dec 13;55(49):6787-6800. PubMed PMID: 27766858.

3. Development and application of ssNMR methods for structural studies of biopolymers.

Although ssNMR is indispensable for obtaining molecular information about the structures and dynamics of insoluble macromolecules, its application is limited by low sensitivity and spectral resolution. To enhance signal-to-noise ratios, I optimized experimental conditions for Dynamic Nuclear Polarization (DNP) of membrane proteins at low temperatures, resulting in 100-fold improvements in signal-to-noise ratios of the NMR data. Additionally, I developed new chemical formulations of model biological membranes that enhance the spectral resolution at low temperatures without disrupting protein structures. Moreover, I applied ssNMR to address various questions about macromolecules, including determining the metal coordination geometry of catalytic fibrils and analyzing the bound water within polymer networks. These methods will be useful in many other experimental studies in the fields of biological and polymer sciences.

a. Baek Y, Lee M. Solid-state NMR spectroscopic analysis for structure determination of a zinc-bound catalytic amyloid fibril. Methods Enzymol. 2024;697:435-471. PubMed PMID: 38816132.
b. Kim S, Lee M, Hong M, Holten-Andersen N. Quantitative Correlation between Bound Water and Mechanical Stress Relaxation in Dehydrated Metal-Coordinate Polymer Networks. Chemistry of materials: a publication of the American Chemical Society. 2022 November 30; 34(23):10329-10337. Available from: https://pubs.acs.org/doi/full/10.1021/acs.chemmater.2c01795 DOI: https://doi.org/10.1021/acs.chemmater.2c01795
c. Liao SY, Lee M, Wang T, Sergeyev IV, Hong M. Efficient DNP NMR of membrane proteins: sample preparation protocols, sensitivity, and radical location. J Biomol NMR. 2016 Mar;64(3):223-37. PubMed Central PMCID: PMC4826309.
d. Lee M, Hong M. Cryoprotection of lipid membranes for high-resolution solid-state NMR studies of membrane peptides and proteins at low temperature. J Biomol NMR. 2014 Aug;59(4):263-77. PubMed Central PMCID: PMC4160392.

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