BIOGRAPHICAL SKETCH

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NAME: Yang, Yang

eRA COMMONS USER NAME (credential, e.g., agency login): yang.yang1

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
Beijing Forestry University, Beijing	BS	07/2011	Life Science
Institute of Biophysics, Chinese Academy of Sciences, Beijing	DPHIL	01/2017	Biochemistry and molecular biology

A. Personal Statement

I am an Assistant Professor in the Structural Biology Department at Van Andel Research Institute (VARI), where I lead a basic science lab dedicated to understanding the structural basis of neurodegenerative diseases. I established my lab in June 2024, focusing my research on the use cryo-electron microscopy/tomography (cryo-EM/ET) to study the structures of native amyloid assemblies isolated from postmortem tissues. With more than a decade of experience in structural biology, I have a proven track record of characterizing structures of challenging biological samples. I completed my postdoctoral fellowship training with Drs. Sjors Scheres and Michel Goedert at the Laboratory of Molecular Biology in Cambridge (UK). I led several pioneering cryo-EM projects that visualized protein filaments associated with Parkinson's disease, Alzheimer's disease, and dementia with Lewy bodies. Specifically, I characterized the first cryo-EM structures of two types of amyloid-β 42 filaments from human brains affected by Alzheimer's disease, as well as α-synuclein filaments from both Parkinson's disease, and dementia with Lewy bodies. My findings revealed key structural differences among these types of filaments, providing crucial insights into the distinct mechanisms of disease presentation and identifying potential therapeutic targets.

My team consists of two postdoctoral researchers and one technician, all with extensive experience in neurodegenerative disease research. I will continue to build upon this strong foundation, utilizing cutting-edge cryo-EM and cryo-ET technologies to explore the structural complexities of amyloid formations. Specifically, this project focuses on α-synuclein pathology, investigating how missense mutations and duplications in the *SNCA* gene influence the formation of amyloid aggregates and affect disease progression. To help us understand their specific contributions to the pathogenesis of familial PD, we also employ cell (e.g., iPSCs) and mouse models.

Throughout my career, I have collaborated with multiple investigators, utilizing cryo-EM, cryo-ET, proteomics, and immunohistochemistry on both human and mouse samples to characterize amyloid structures, leading to several publications. Our long-term goal is to translate these structural insights into actionable strategies for early diagnosis and effective treatments, ultimately enhancing our understanding of PD and other neurodegenerative diseases like Alzheimer's disease and other types of dementias, contributing to the development of innovative therapeutic approaches for these devastating diseases.

I have both the expertise and resources necessary for the completion of the proposed research. In addition, I have gathered a team of collaborators that with complementary expertise and resources to guarantee the successful completion of this project.

The following peer-reviewed publications summarize relevant expertise for this project:

a. **Yang Y**, Garringer HJ, Shi Y, Lövestam S, Peak-Chew S, Zhang X, Kotecha A, Bacioglu M, Koto A, Takao M, Spillantini MG, Ghetti B, Vidal R, Murzin AG, Scheres SHW, Goedert M. New SNCA

mutation and structures of α-synuclein filaments from juvenile-onset synucleinopathy. *Acta Neuropathol*. 2023 May;145(5):561-572. PubMed Central PMCID: PMC10119069.

b. **Yang Y**, Shi Y, Schweighauser M, Zhang X, Kotecha A, Murzin AG, Garringer HJ, Cullinane PW, Saito Y, Foroud T, Warner TT, Hasegawa K, Vidal R, Murayama S, Revesz T, Ghetti B, Hasegawa M, Lashley T, Scheres SHW, Goedert M. Structures of α-synuclein filaments from human brains with Lewy pathology. *Nature*. 2022 Oct;610(7933):791-795. PubMed Central PMCID: PMC7613749.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2024 -	Assistant Professor, Department of Structural Biology, Van Andel Institute, Grand Rapids, MI
2020 - 2024	Career Development Fellow, MRC Laboratory of Molecular Biology, Cambridge
2017 - 2020	Research Associate, Institute of Biophysics, Chinese Academy of Sciences, Beijing

Honors

2023	Junior Faculty Award, 17th International Conference on AD/PD
2022-2023	Outstanding Level End of Year SAS Award, MRC Laboratory of Molecular Biology
2021	Oral Presentation Award, 27th Annual Conference of CLSS-UK
2016	Outstanding Student Speaker, 4th iHuman Forum
2016	Best Poster Award, World Life Science Conference
2014	Merit Student Award, Chinese Academy of Life Sciences

C. Contribution to Science

1. **Defining structural characteristics of α-synuclein filaments.** I identified the Lewy fold of α-synuclein filaments from the brains of individuals with PD and dementia with Lewy bodies. Despite the challenge of non-twist filaments being impossible to solve with helical reconstruction, I successfully characterized a minority of twisted filaments and solved their structures, termed the Lewy fold. I discovered that both twisted and untwisted filaments adopt the same Lewy fold, which differs from the folds of multiple system atrophy. This work was published in Nature in 2022. Additionally, I investigated a case of Juvenile-Onset Synucleinopathy with 7 residues insertion in the α-synuclein, revealing two types of α-synuclein filaments distinct from those in PD, dementia with Lewy bodies, and multiple system atrophy. These studies enhance our understanding of amyloid formation and disease progression.

    a. Yang Y, Garringer HJ, Shi Y, Lövestam S, Peak-Chew S, Zhang X, Kotecha A, Bacioglu M, Koto A, Takao M, Spillantini MG, Ghetti B, Vidal R, Murzin AG, Scheres SHW, Goedert M. New SNCA mutation and structures of α-synuclein filaments from juvenile-onset synucleinopathy. Acta Neuropathol. 2023 May;145(5):561-572. PubMed Central PMCID: PMC10119069.

    b. Yang Y, Shi Y, Schweighauser M, Zhang X, Kotecha A, Murzin AG, Garringer HJ, Cullinane PW, Saito Y, Foroud T, Warner TT, Hasegawa K, Vidal R, Murayama S, Revesz T, Ghetti B, Hasegawa M, Lashley T, Scheres SHW, Goedert M. Structures of α-synuclein filaments from human brains with Lewy pathology. Nature. 2022 Oct;610(7933):791-795. PubMed Central PMCID: PMC7613749.

2. **Understanding the basis of amyloid aggregation in Alzheimer's disease**. I have significantly advanced the field's understanding of amyloid filaments in Alzheimer's disease. For decades, the structural details of Aβ42 filaments from human brains remained elusive. I pioneered new extraction methods and led initiatives to obtain insoluble aggregates, successfully resolving two high-resolution structures of Aβ42 filaments with S-shaped folds. Utilizing techniques such as immunohistochemistry, immunolabeling, and mass spectrometry, I thoroughly characterized these amyloid features. Additionally, I determined the Aβ42 filament structure from AppNL-F knock-in mice, an animal model with amyloid filament structures akin to those in human brains. This work, published in *Science* in January 2022 and highlighted by a perspective article in the same issue, represents a significant milestone in the field. I have also explored familial Alzheimer's disease mutations, obtaining high-resolution cryo-EM structures of Aβ filaments from a case with the Arctic

mutation. This revealed that the E22G mutation enhances hydrogen bonding and promotes filament formation, advancing our knowledge of familial AD. Through the aqueous extraction method, we discovered that short filaments have neuronal toxicity, which also can be recognized by the FDA-approved antibody lecanemab. My research profoundly enhances our understanding of Alzheimer's disease pathophysiology.

a. **Yang Y**, Murzin AG, Peak-Chew S, Franco C, Garringer HJ, Newell KL, Ghetti B, Goedert M, Scheres SHW. Cryo-EM structures of Aβ40 filaments from the leptomeninges of individuals with Alzheimer's disease and cerebral amyloid angiopathy. *Acta Neuropathol Commun*. 2023 Dec 4;11(1):191. PubMed Central PMCID: PMC10694933.
b. Stern AM, **Yang Y**, Jin S, Yamashita K, Meunier AL, Liu W, Cai Y, Ericsson M, Liu L, Goedert M, Scheres SHW, Selkoe DJ. Abundant Aβ fibrils in ultracentrifugal supernatants of aqueous extracts from Alzheimer's disease brains. *Neuron.* 2023 Jul 5;111(13):2012-2020.e4. PubMed Central PMCID: PMC10330525.
c. **Yang Y**, Zhang W, Murzin AG, Schweighauser M, Huang M, Lövestam S, Peak-Chew SY, Saito T, Saido TC, Macdonald J, Lavenir I, Ghetti B, Graff C, Kumar A, Nordberg A, Goedert M, Scheres SHW. Cryo-EM structures of amyloid-β filaments with the Arctic mutation (E22G) from human and mouse brains. *Acta Neuropathol*. 2023 Mar;145(3):325-333. PubMed Central PMCID: PMC9925504.
d. **Yang Y**, Arseni D, Zhang W, Huang M, Lövestam S, Schweighauser M, Kotecha A, Murzin AG, Peak-Chew SY, Macdonald J, Lavenir I, Garringer HJ, Gelpi E, Newell KL, Kovacs GG, Vidal R, Ghetti B, Ryskeldi-Falcon B, Scheres SHW, Goedert M. Cryo-EM structures of amyloid-β 42 filaments from human brains. *Science*. 2022 Jan 14;375(6577):167-172. PubMed Central PMCID: PMC7612234.

3. **Defining tautopathies from the structural point of view.** I contributed to the structure-based classification of tauopathies, published in Nature in September 2021. This work provided a hierarchical classification of tauopathies based on filament folds, enhancing clinical diagnosis and neuropathology, and defining new disease forms. Additionally, I co-identified TMEM106B filaments in the brains of individuals with various neurodegenerative diseases, finding that they form in an age-dependent manner with these results published in Nature in 2022.

a. Schweighauser M, Arseni D, Bacioglu M, Huang M, Lövestam S, Shi Y, **Yang Y**, Zhang W, Kotecha A, Garringer HJ, Vidal R, Hallinan GI, Newell KL, Tarutani A, Murayama S, Miyazaki M, Saito Y, Yoshida M, Hasegawa K, Lashley T, Revesz T, Kovacs GG, van Swieten J, Takao M, Hasegawa M, Ghetti B, Spillantini MG, Ryskeldi-Falcon B, Murzin AG, Goedert M, Scheres SHW. Age-dependent formation of TMEM106B amyloid filaments in human brains. *Nature*. 2022 May;605(7909):310-314. PubMed Central PMCID: PMC9095482.
b. Shi Y, Zhang W, **Yang Y**, Murzin AG, Falcon B, Kotecha A, van Beers M, Tarutani A, Kametani F, Garringer HJ, Vidal R, Hallinan GI, Lashley T, Saito Y, Murayama S, Yoshida M, Tanaka H, Kakita A, Ikeuchi T, Robinson AC, Mann DMA, Kovacs GG, Revesz T, Ghetti B, Hasegawa M, Goedert M, Scheres SHW. Structure-based classification of tauopathies. *Nature*. 2021 Oct;598(7880):359-363. PubMed Central PMCID: PMC7611841.

4. **Studying ligand-biased relationships of the hydrocarboxylic acid receptor.** I investigated the structure and ligand-biased relationships of the hydrocarboxylic acid receptor (HCA2), which is a G protein-coupled receptor that regulates lipid metabolism, including cholesterol levels, and plays a role in immune response and inflammation implicated in AD and PD. I characterized the cryo-EM structure of the HCA2-Gi signaling complex with the agonist MK-6892, providing a comprehensive pharmacological analysis that revealed the ligand binding mode, activation, and signaling mechanisms of HCA2.

a. **Yang Y**, Kang HJ, Gao R, Wang J, Han GW, DiBerto JF, Wu L, Tong J, Qu L, Wu Y, Pileski R, Li X, Zhang XC, Zhao S, Kenakin T, Wang Q, Stevens RC, Peng W, Roth BL, Rao Z, Liu ZJ. Structural insights into the human niacin receptor HCA2-G(i) signalling complex. *Nat Commun*. 2023 Mar 27;14(1):1692. PubMed Central PMCID: PMC10043007.

Complete List of Works in MyBibliography

https://www.ncbi.nlm.nih.gov/myncbi/yang.yang.83/bibliography/public/

Van Andel Research Institute
Current and Pending Support – Brain Research Foundation Seed Grant Program

Name of Individual: Yang, Yang
Commons ID: yang.yang1

Other Support – Project/Proposal:

ACTIVE
None

PENDING
Title: Diffusible Aβ Aggregates in Alzheimer's Disease Brain

Major Goals: The major goals of this proposal are to redefine the pathogenic role of Aβ aggregates in Alzheimer's disease by challenging the current paradigm that protofibrils/oligomers, rather than fibrils, drive disease progression. By focusing on diffusible Aβ fibrils in interstitial fluid as the key mediators of toxicity, the study aims to determine how their structure, diffusion dynamics, and interactions with APOE genotype and anti-amyloid antibodies contribute to AD pathology.

Status of Support: Pending

Project Number: N/A

Name of PD/PI: Stern, Andrew

Source of Support: National Institute of Neurological Disorders and Stroke/The Brigham and Women's Hospital, Inc. Subaward

Primary Place of Performance: Van Andel Research Institute

Project/Proposal Start and End Date: 07/2025 – 06/2030

Total Award Amount (including Indirect Costs): $1,152,000

Person Months (Calendar/Academic/Summer) per budget period:

Year (YYYY)	Person Months (##.##)
2026	1.2 CM
2027	1.2 CM
2028	1.2 CM
2029	1.2 CM
2030	1.2 CM

Title: Structural basis of plaque morphogenesis in Alzheimer disease

Major Goals: This research aims to investigate the structural basis of Aβ plaque morphogenesis across different Thal stages and animal models to improve our understanding of AD pathology and contribute to the development of novel approaches for early detection and intervention.

Status of Support: R01NS144991

Project Number: N/A

Name of PD/PI: Yang, Yang

Source of Support: National Institute of Neurological Disorders and Stroke

Primary Place of Performance: Van Andel Research Institute

Project/Proposal Start and End Date: 07/2025 – 06/2030

Total Award Amount (including Indirect Costs): $3,497,455

Name of Individual: Yang, Yang
Commons ID: yang.yang1

Person Months (Calendar/Academic/Summer) per budget period:

Year (YYYY)	Person Months (##.##)
2026	3.6 CM
2027	3.6 CM
2028	3.6 CM
2029	3.6 CM
2030	3.6 CM

Title: Utilizing Cryo-EM to Advance Amyloid-Targeted Diagnosis and Treatment for Alzheimer's Disease.

Major Goals: The major goals are to focus on characterizing protein aggregates directly from brain tissue at atomic-level resolution using cryo-EM and cryo-electron tomography (cryo-ET.) Additionally, the aim is to characterize fibrils complexed with PET tracers and antibodies to advance amyloid-specific diagnostic and therapeutic development.

Status of Support: Pending

Project Number: N/A

Name of PD/PI: Yang, Yang

Source of Support: The Esther A. & Joseph Klingenstein Fund, Inc.

Primary Place of Performance: Van Andel Research Institute

Project/Proposal Start and End Date: 07/2025 – 6/2028

Total Award Amount (including Indirect Costs): $300,000.

Person Months (Calendar/Academic/Summer) per budget period:

Year (YYYY)	Person Months (##.##)
2026	0.0 CM
2027	0.0 CM
2028	0.0 CM

* Fellowship would be awarded to the institution to be used over a three-year period for any activity, including (but not limited to) salary support, research assistants, equipment, or any other purpose that promotes the scientific activities of the Klingenstein Neuroscience Fellow.

IN-KIND

NONE

Overlap (summarized): The proposals do not overlap.

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Signature/Date: Signed by: Yang Yang FF6AE1A288904F4... 3/28/2025 | 10:41 EDT

This document has been digitally signed by the attesting individual in alignment with institutional practices for NIH Other Support. Supporting documentation for reasonable authentication is available upon request.