UNIVERSITY OF MINNESOTA
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CJD Foundation, Washington DC, November 13, 2024

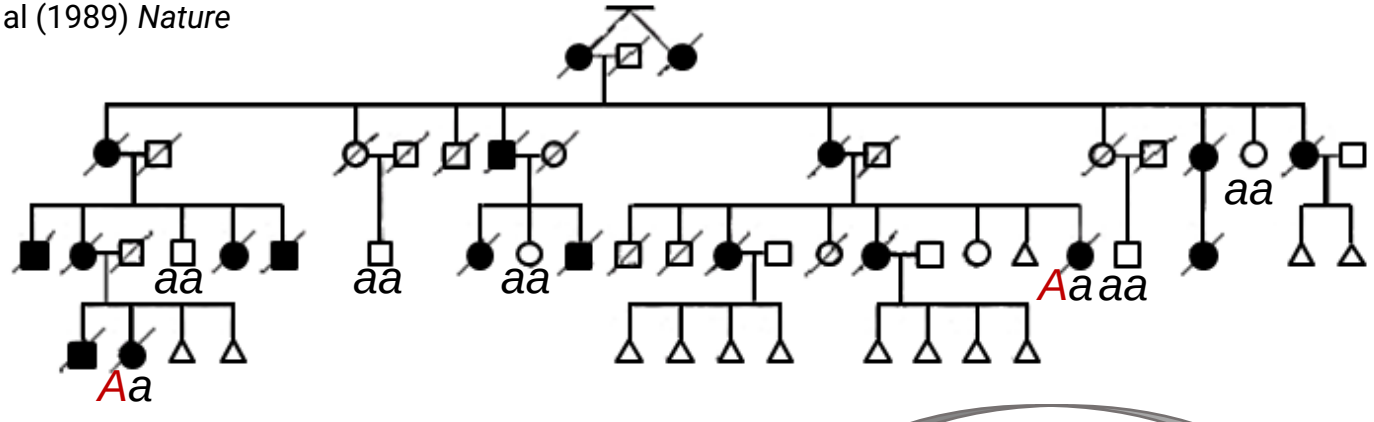
THE Aβ OLIGOMER Aβ*56 APPEARS TO ASSEMBLE INTO HOLLOW SPHEROID STRUCTURES

Karen Hsiao Ashe, Professor of Neurology

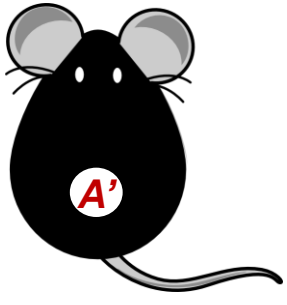
Grossman Center for Memory Research and Care
University of Minnesota Medical School

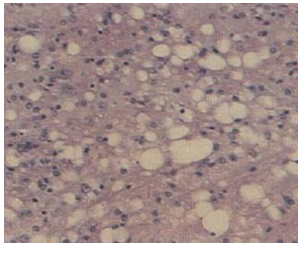
GSS is Horizontally and Vertically Transmitted

Hsiao et al (1989) *Nature*

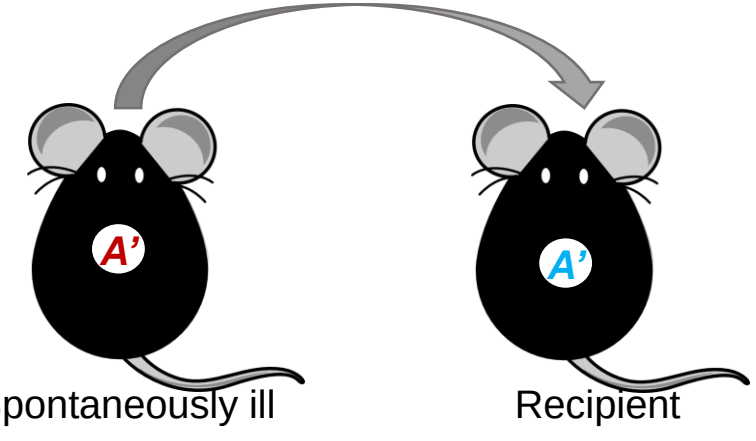


A = PrP codon 102 proline → leucine
a = PrP wild-type



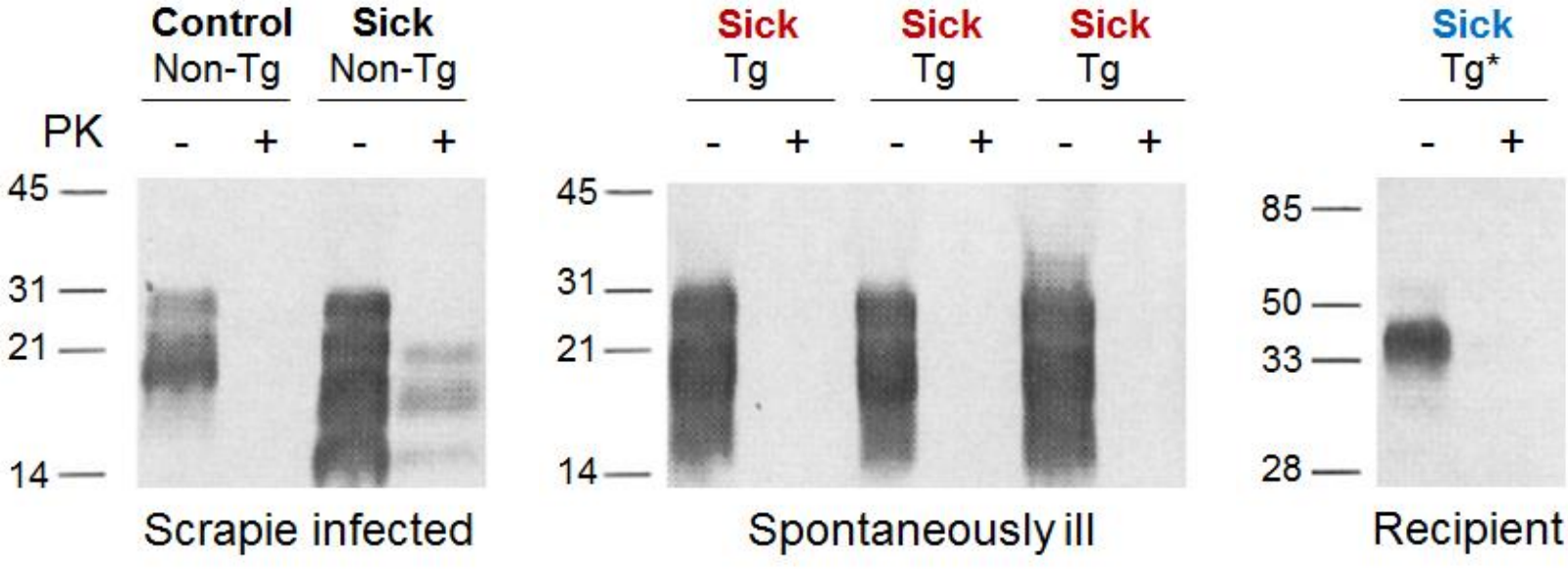


Hsiao et al (1990) *Science*



Hsiao et al (1994) *PNAS*
Telling et al (1996) *Genes & Development*

Can Illness Occur in the Absence of Amyloid?



PK = Proteinase K *Inoculated low PrP_{P101L}-expressing mouse

A curious dissociation between amyloid and illness

Hsiao et al (1994) *PNAS*

Aβ*56 Correlates with Aging or Memory Loss in Studies from Several Independent Labs

- **Humans**
  - Yoo et al (Moon), *Sci Reports*, 2020
  - Lapcinski et al (Liu), in prep*

- **Mice**
  - [Lesné et al (Ashe), *Nature*, 2006*]
  - Billings et al (LaFerla), *J Nsci*, 2007
  - Cheng et al (Mucke), *JBC*, 2007*
  - Meilandt et al (Mucke), *J Nsci*, 2009*
  - Liu et al (Pasinetti), *J Nsci*, 2008*
  - Castillo-Carranza et al (Kayed), *J Nsci*, 2015*
  - Liu et al (Ashe), *Cell Reports*, 2015*
  - Liu et al (Liu), *iScience*, 2024

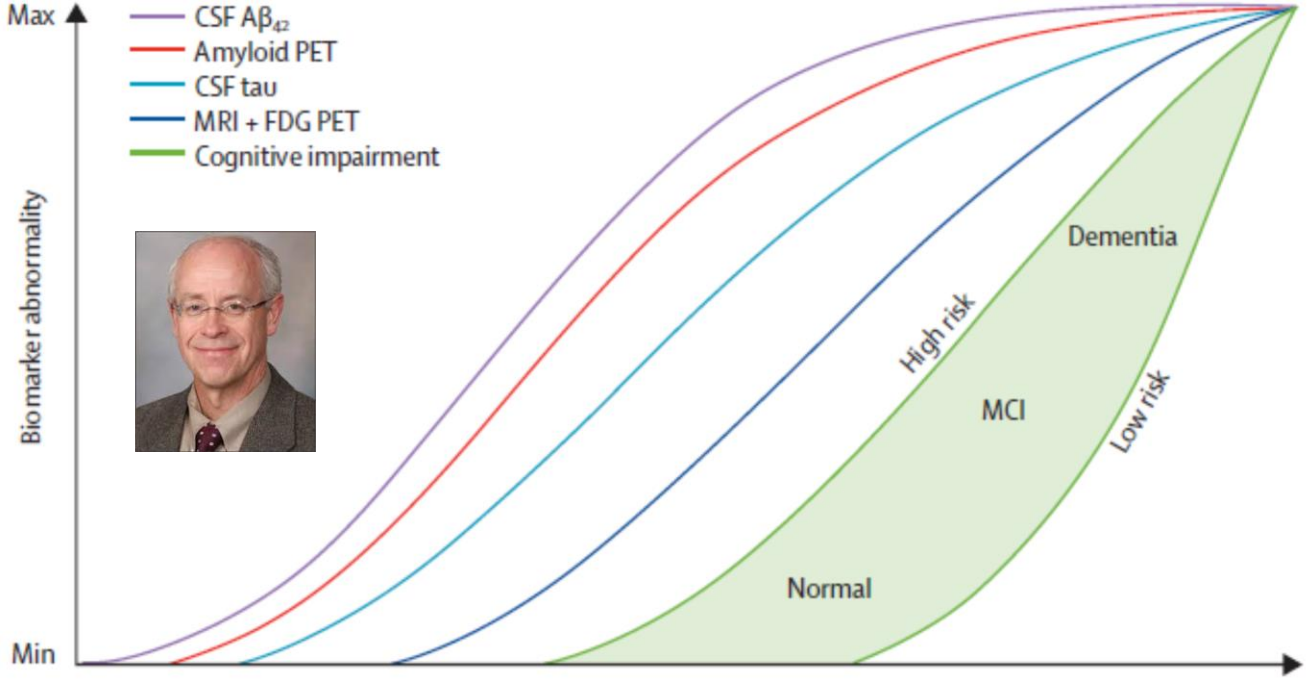
- **Dogs**
  - Pop et al (Cotman), *Neurobiol Aging*, 2012

Outline

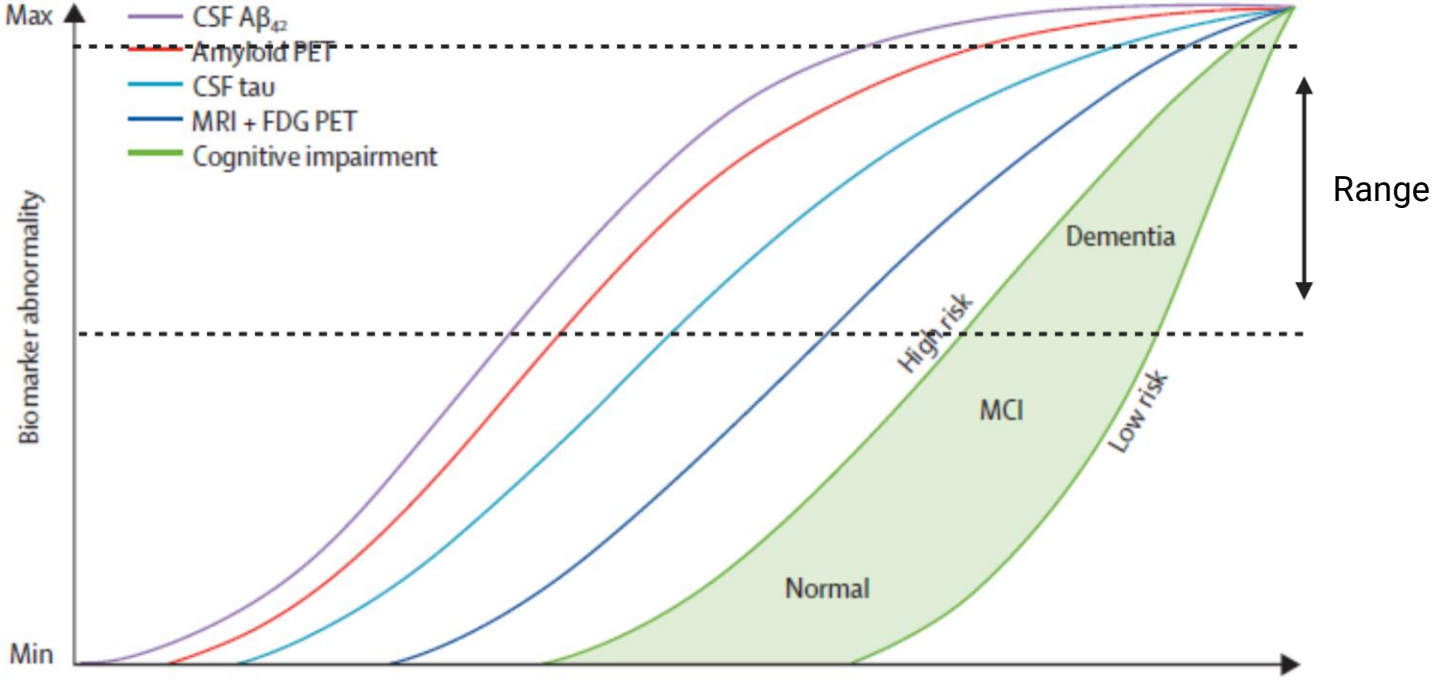
1. Aβ*56's relationship to cognition in humans
2. Biochemical characteristics of human Aβ*56
3. Isolation of Aβ*56
4. Low resolution structure of Aβ*56

1. Aβ*56's Relationship to Cognition in Humans

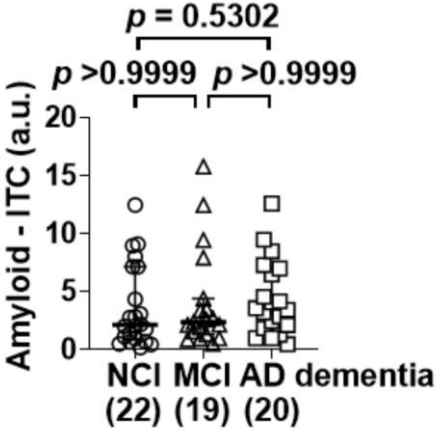
Natural History of Alzheimer's Dementia



Amyloid Plaques Appear before Cognitive Impairment



Aβ*56 is 2-4 Times Higher in AD Independently of Plaque Load



ROSMAP

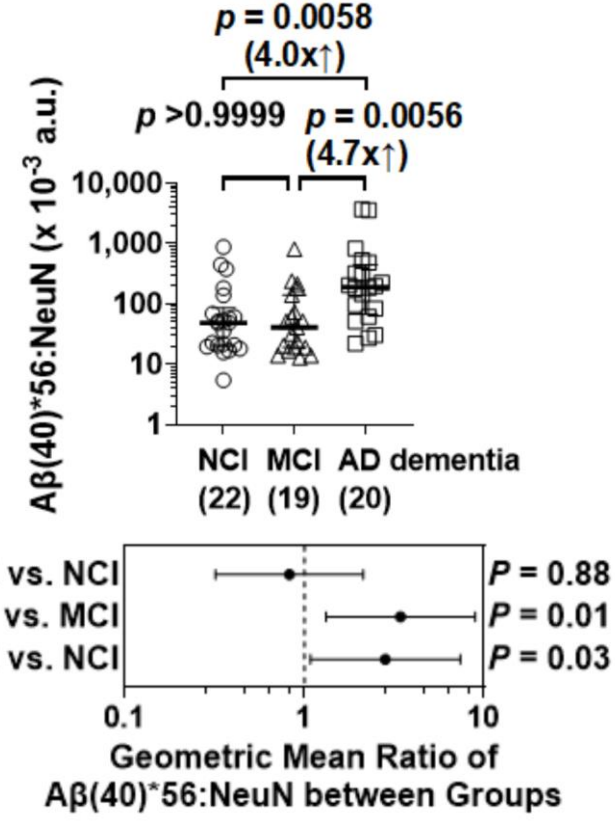
Inferior Temporal Cortex (ITC)

Ian Lapcinski
Peng Liu
Ashley Petersen

Aβ*56 is 2-4 Times Higher in AD Independently of Plaque Load

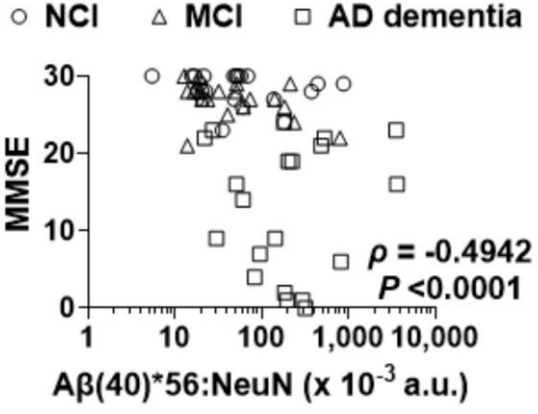
ROSMAP

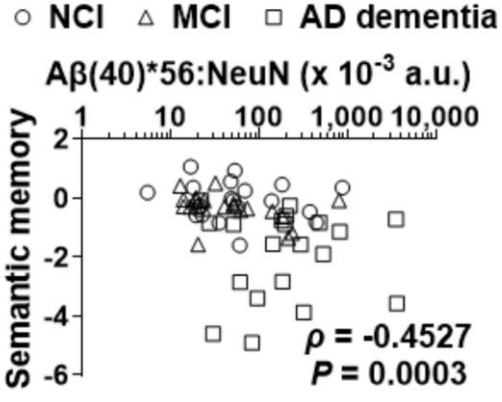
Inferior Temporal Cortex (ITC)

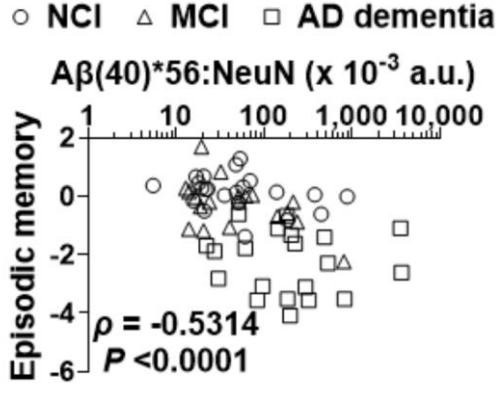


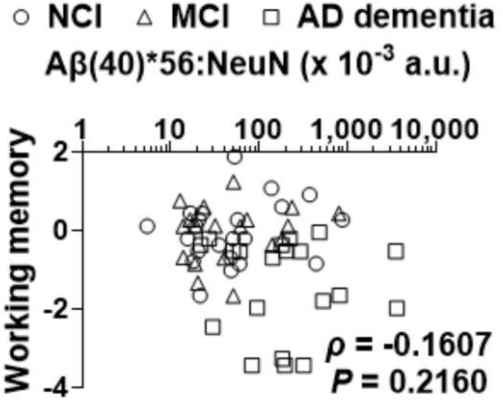
Ian Lapcinski
Peng Liu
Ashley Petersen

Aβ*56 Correlates Inversely with Cognitive Measures





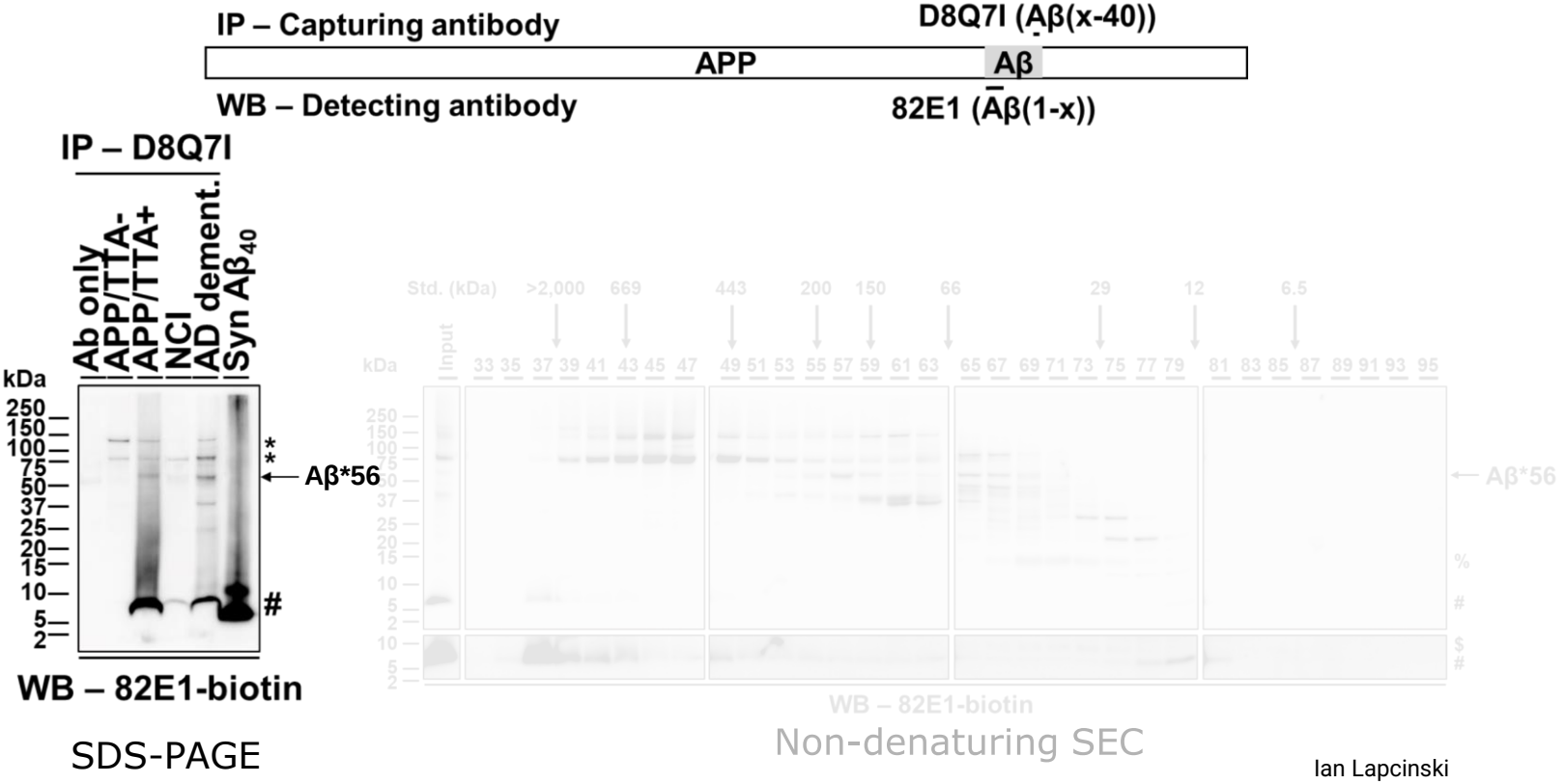




Ian Lapcinski
Peng Liu
Ashley Petersen

2. Biochemical Characteristics of Aβ*56

Human and Mouse Aβ*56 Contains Canonical Aβ and Migrates at ~56 kDa under Denaturing and Non-denaturing Conditions



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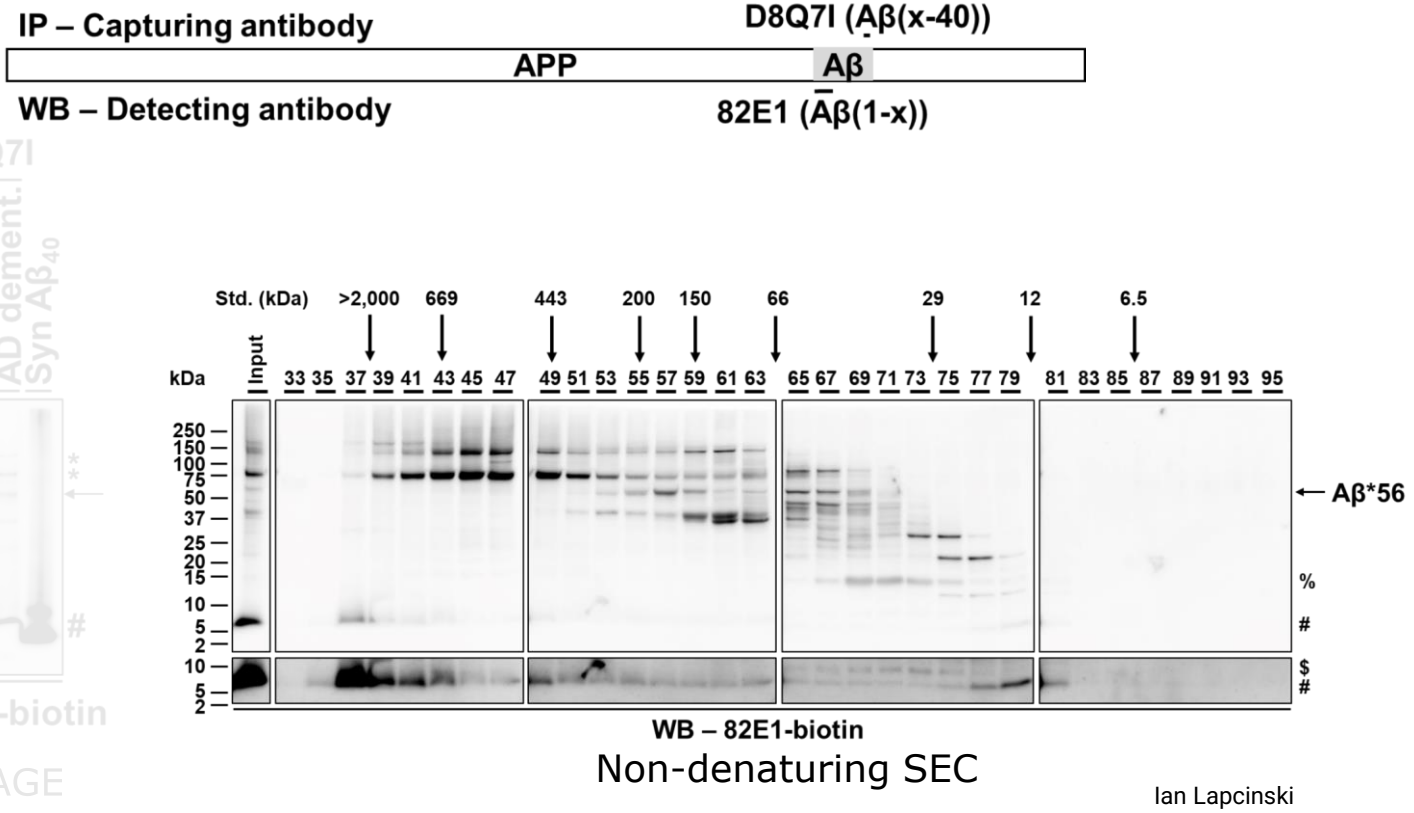
Human and Mouse Aβ*56 Contains Canonical Aβ and Migrates at ~56 kDa under Denaturing and Non-denaturing Conditions



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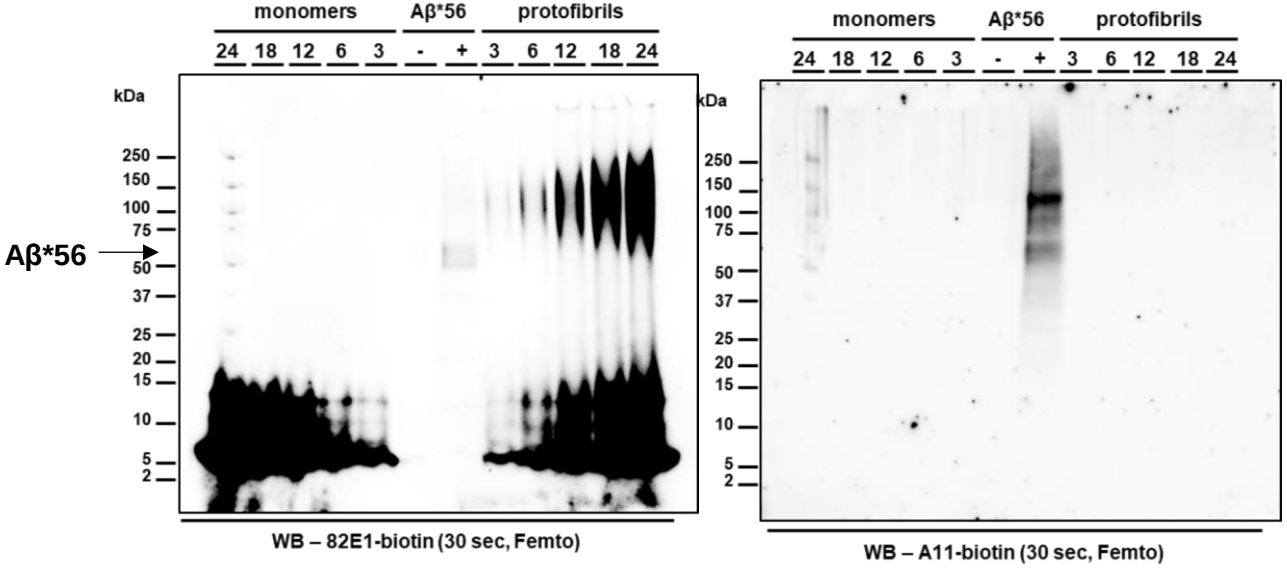
Human Aβ*56 Binds A11 Antibodies



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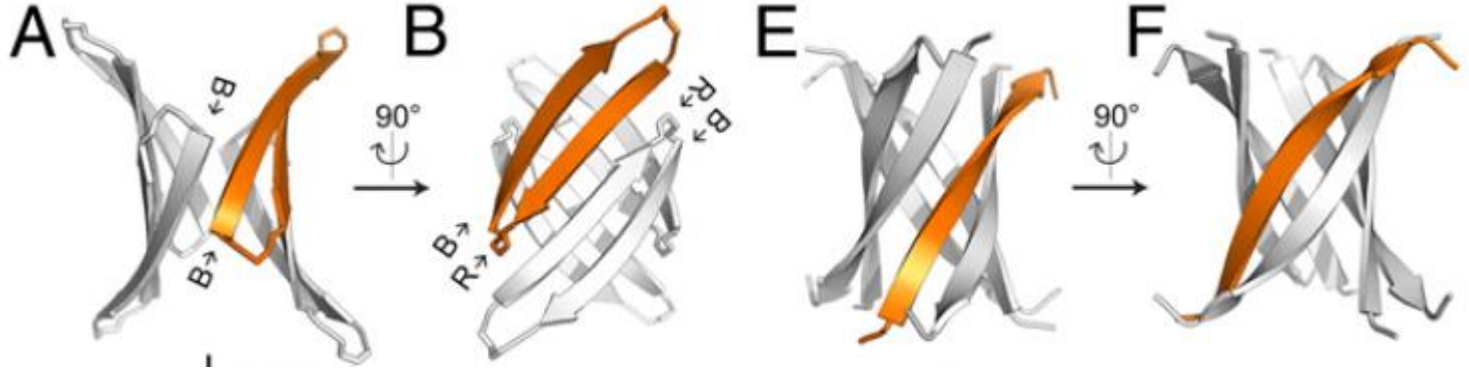
Toxic Aggregates with Out-of-Register β-Sheets Bind A11 Antibodies

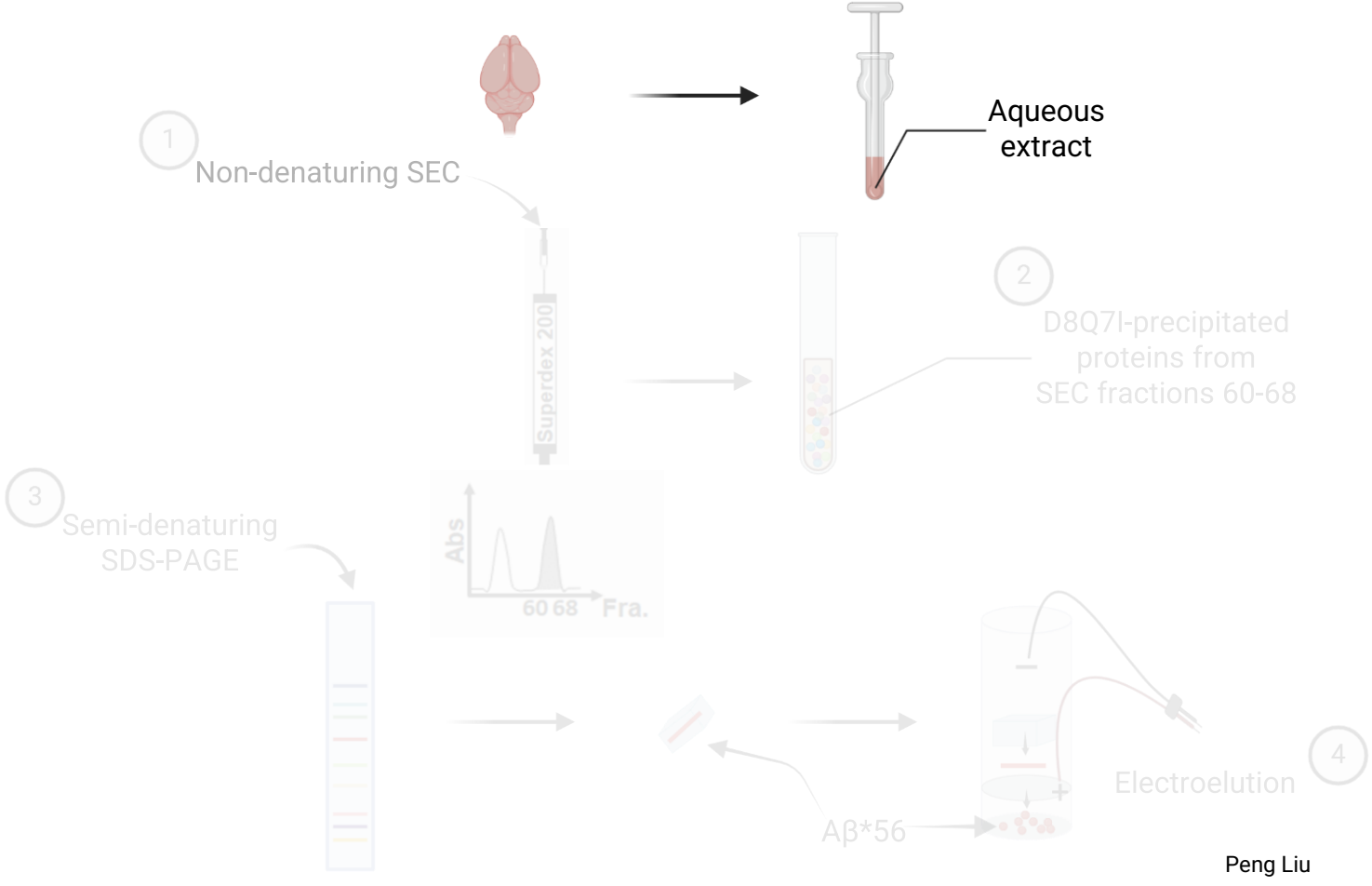


Aβ(30-36) αB crystallin(68-162)

Liu et al (Eisenberg) “Out-of-register beta-sheets suggest a pathway to toxic amyloid aggregates” *PNAS* 2012

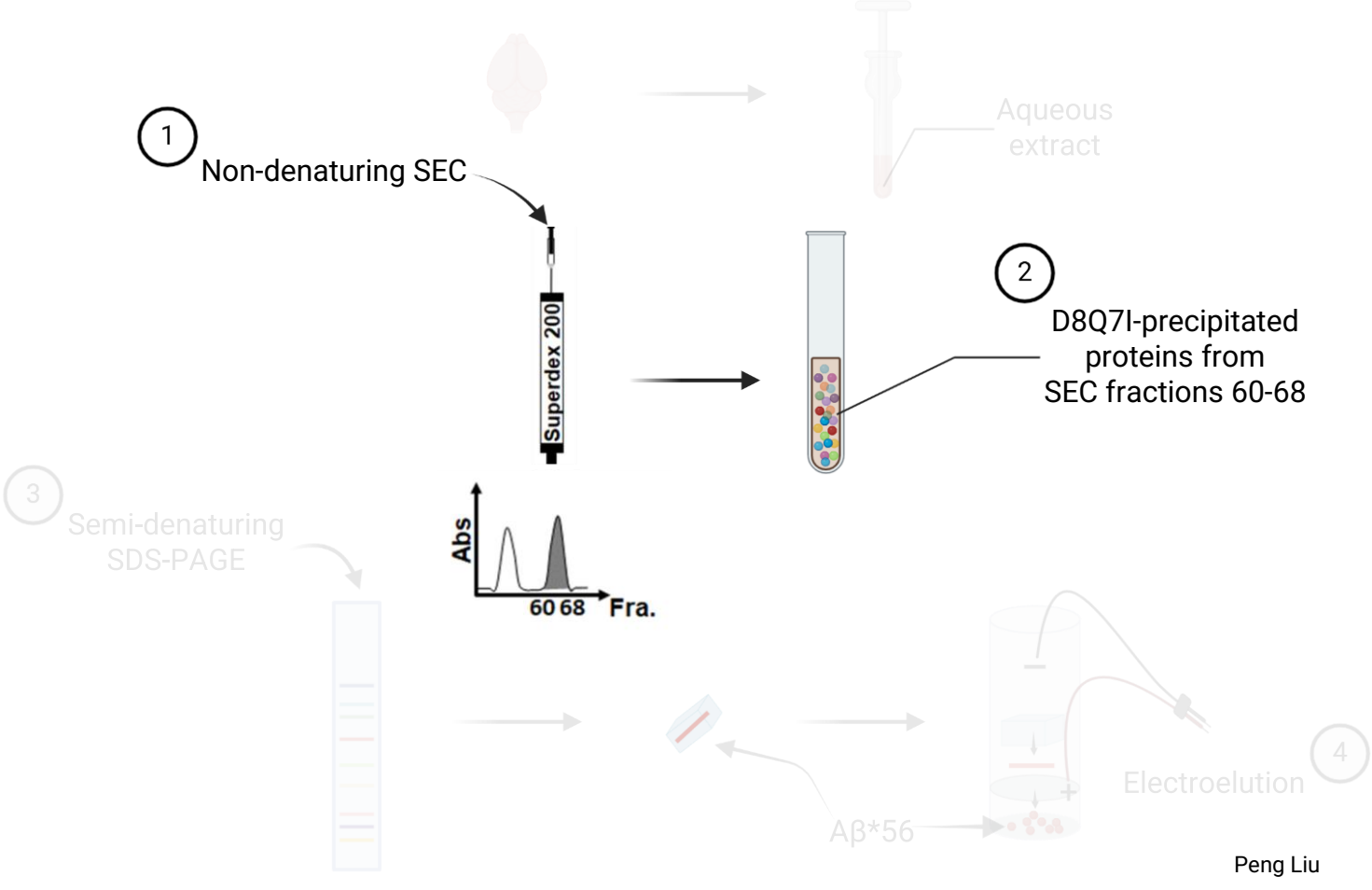
3. Isolation of Aβ*56

Isolation of Aβ*56



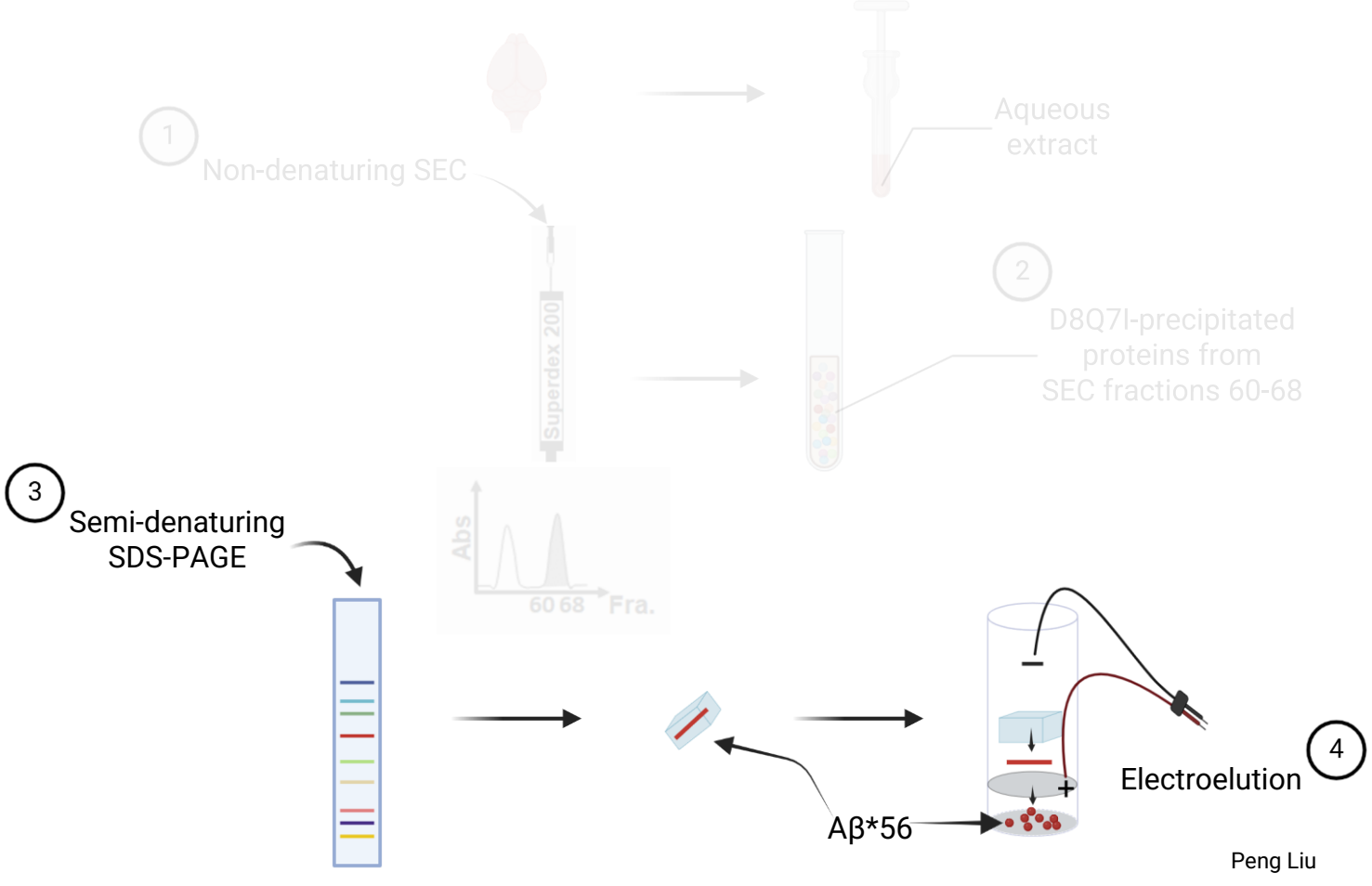
Peng Liu

Isolation of Aβ*56



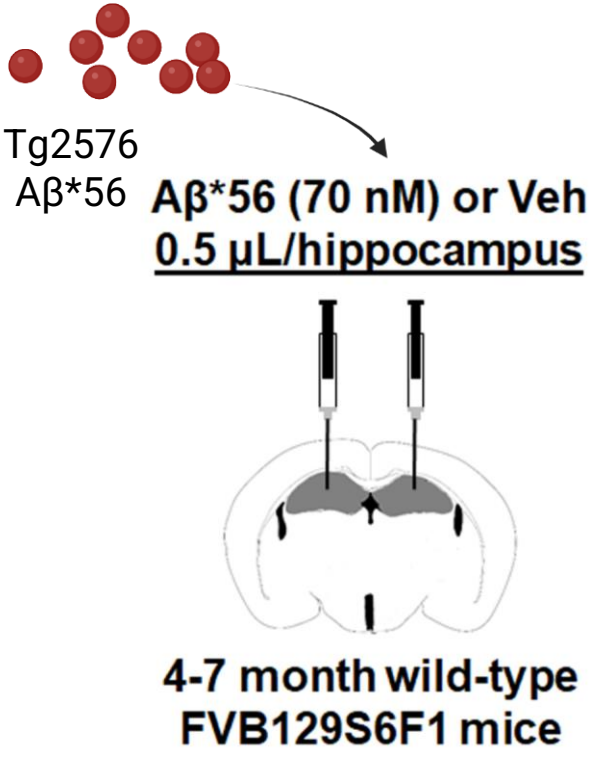
Peng Liu

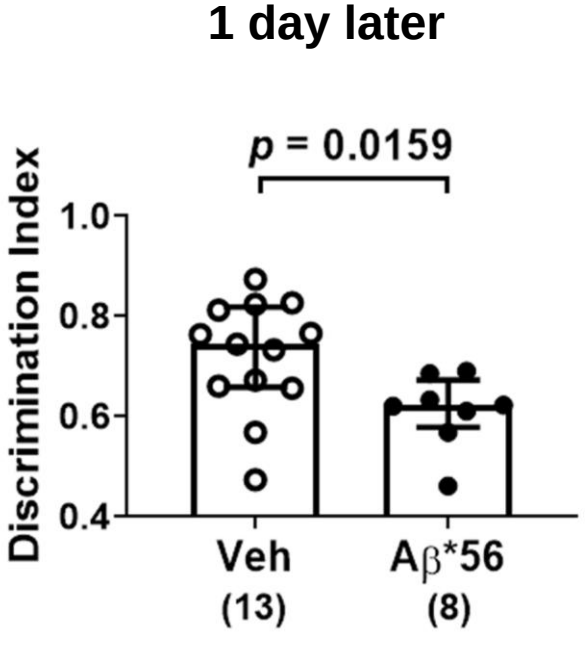
Isolation of Aβ*56



Peng Liu

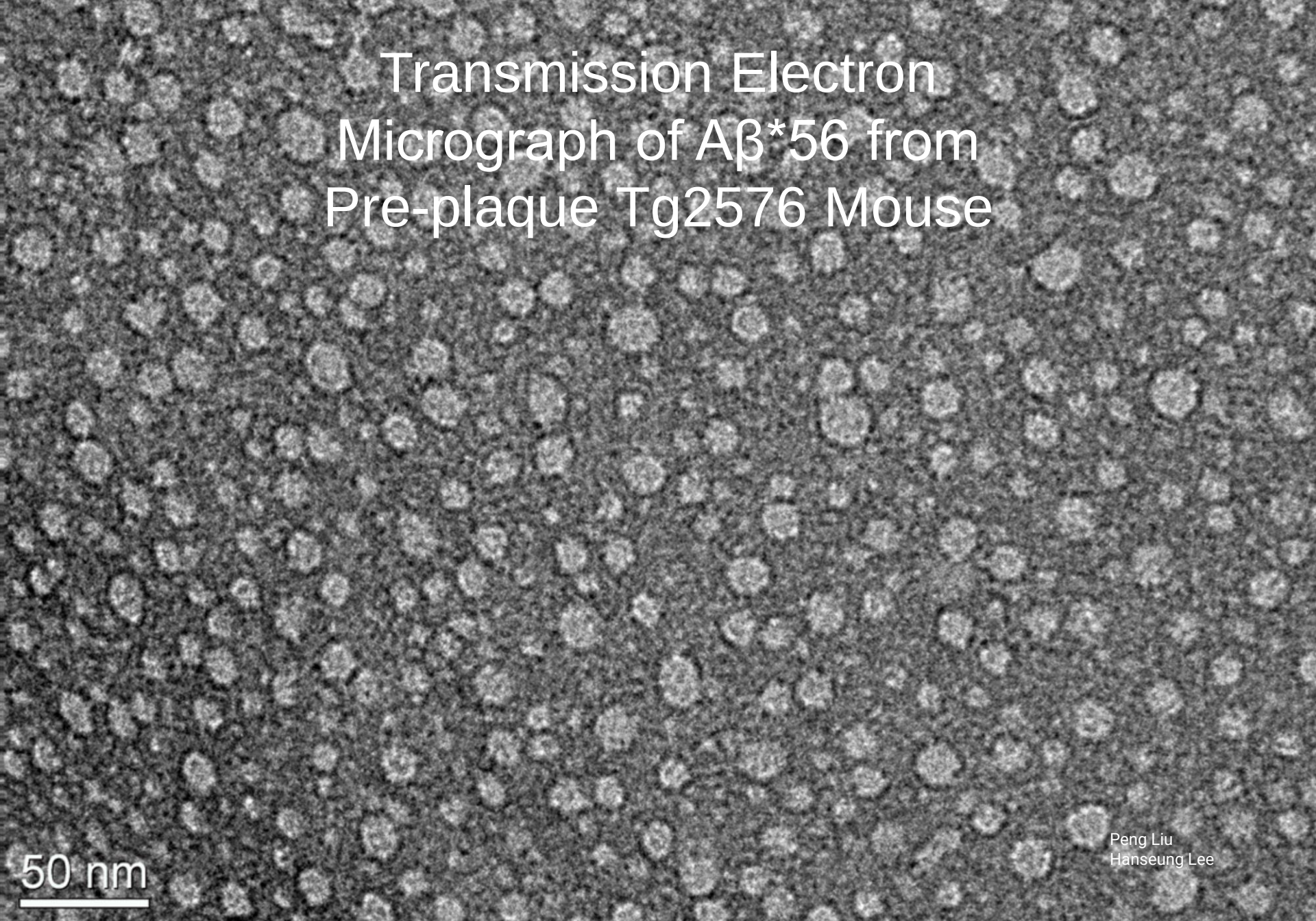
Aβ*56 Impairs Memory Function



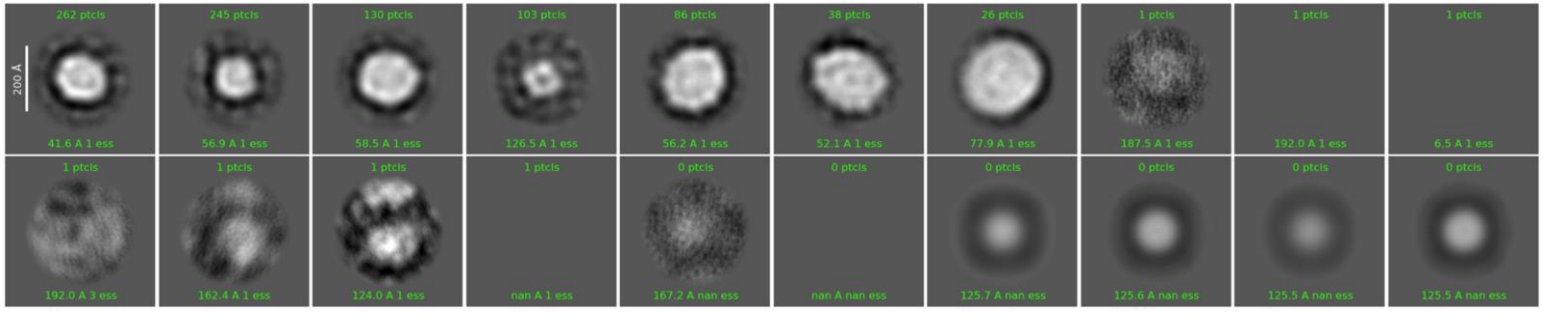


Liu *et al iScience* (2024)

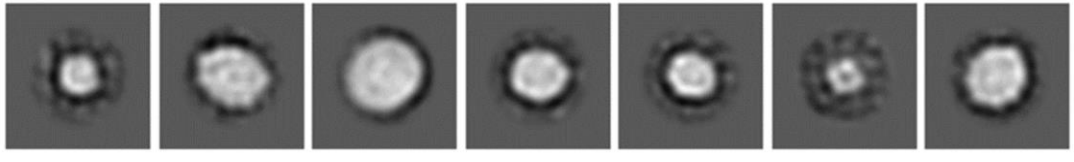
4. Structure of Aβ*56


Transmission Electron Micrograph of Aβ*56 from Pre-plaque Tg2576 Mouse
50 nm
Peng Liu
Hanseung Lee

2D Classification

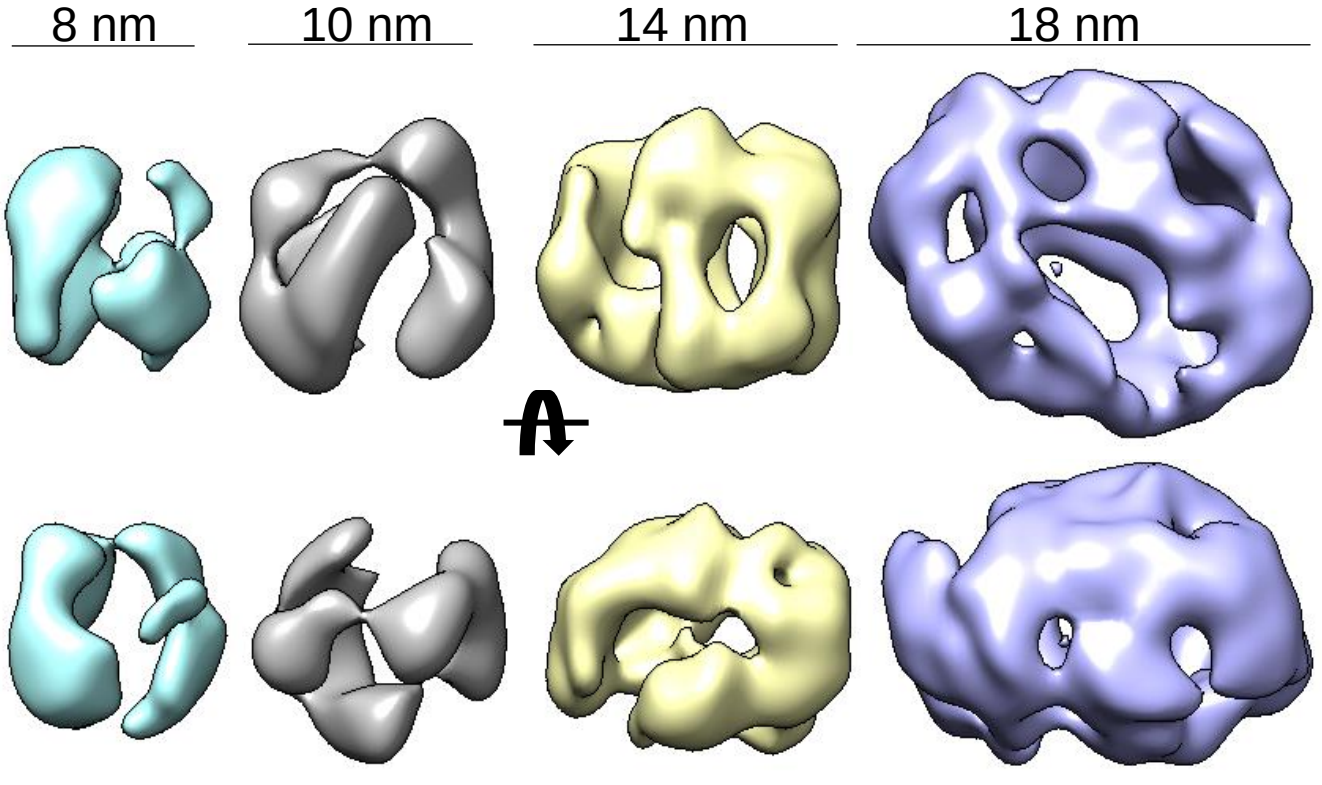


890 particles selected



David Boyer

Ab initio 3D Classification

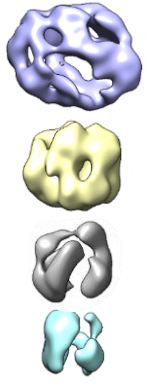


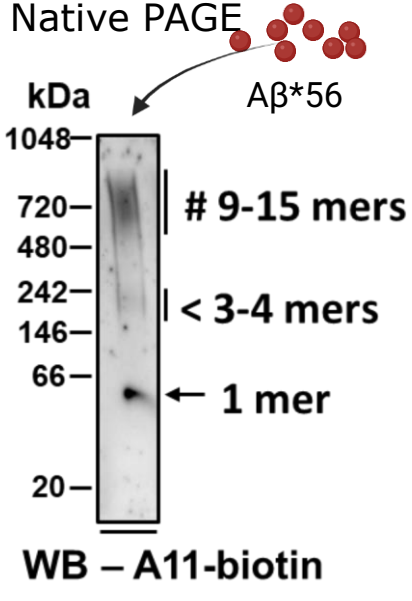
"… a program used by CryoEM software to convert 2D classes to an initial guess of the 3D map. It requires no prior knowledge."

David Boyer

Estimated Mass

Particles (N)	Threshold	Estimated mass (kDa)
470	0.536-0.833	558-1028
230	0.579-0.808	371-543
70	0.866-1.02	171-277
64	1.07-1.3	80-152





"mers" refers to units of Aβ*56

David Boyer
Peng Liu

Summary

Aβ*56 correlates with memory impairment independently of amyloid plaques in humans

Aβ*56 can be reliably and reproducibly isolated using a procedure involving 4 purification steps: SEC, IAP, SDS-PAGE, Electro-elution

Ab initio modeling classified Aβ*56 particles into four groups of 3D structures resembling hollow spheres

Future Studies

We currently lack high-resolution structures of Aβ oligomers that do not contain in-register beta sheets.

High-resolution structures of Aβ*56 could reveal the biophysical basis by which the arrangement of Aβ in an Aβ oligomer evades forming fibrils.

Targeting non-fibrillar Aβ oligomers such as Aβ*56 could lead to new, complementary Aβ therapies that augment the effects of existing anti-Aβ therapies.

Thank you!

University of Minnesota

Peng Liu
Ian Lapcinski
Hanseung Lee
Ashley Petersen
Karen Ashe
Lisa Kemper
Chris Hlynialuk
Beth Steuer
Tommy Loude Jr

University of California Los Angeles

David Eisenberg
David Boyer

MetLife Award (2005)
Royalties Tg2576 mice
Gift (Liu)

To receive a 39-page protocol for the detection and purification of Aβ*56, please write to: liuxx726@umn.edu

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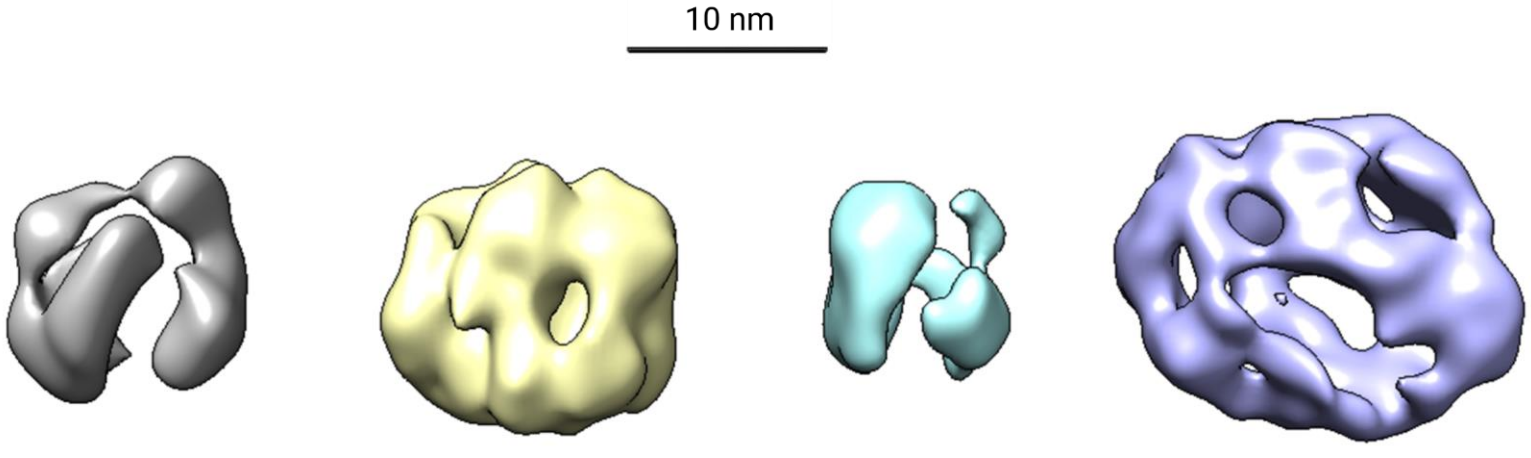
3D Classification



269-342 nm^3

458-670 nm^3

99-187 nm^3

690-1270 nm^3

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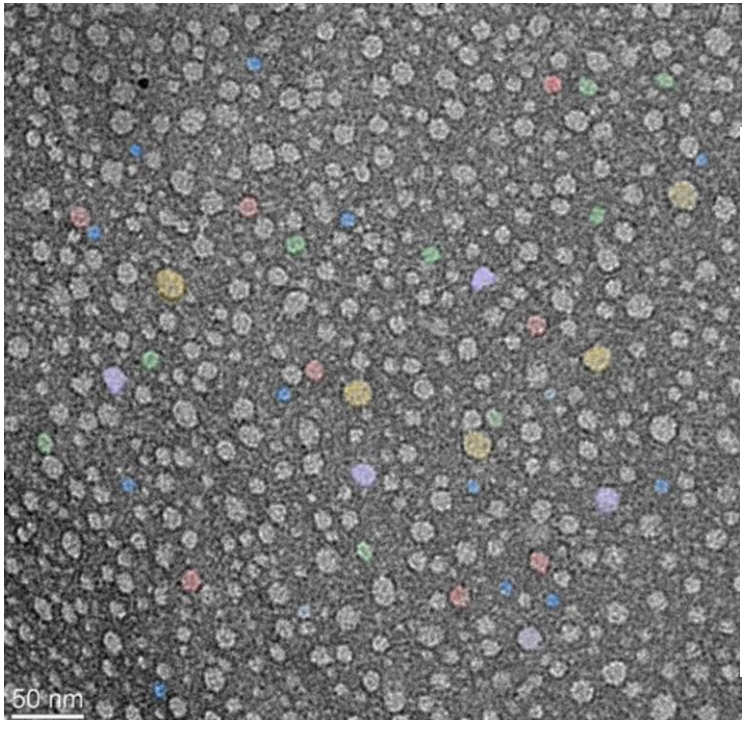
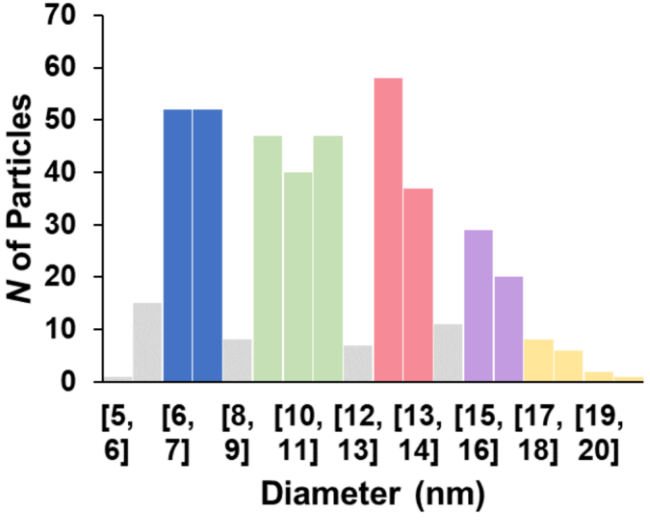
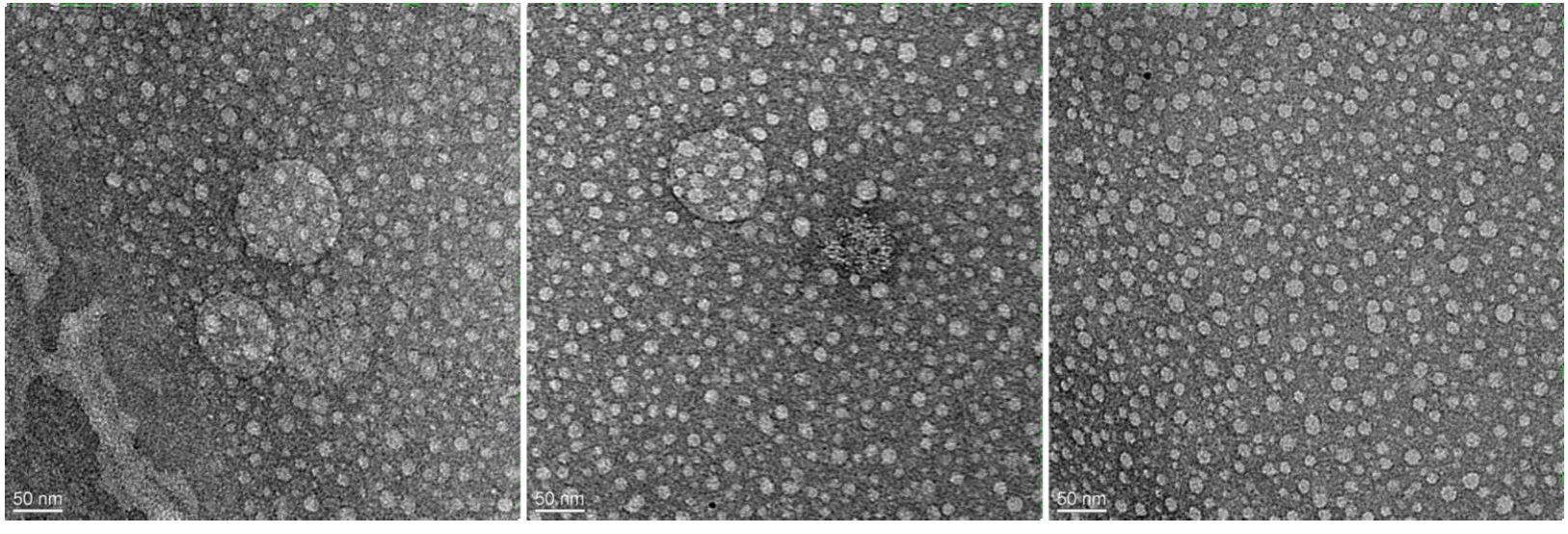
Size-distribution of Particles

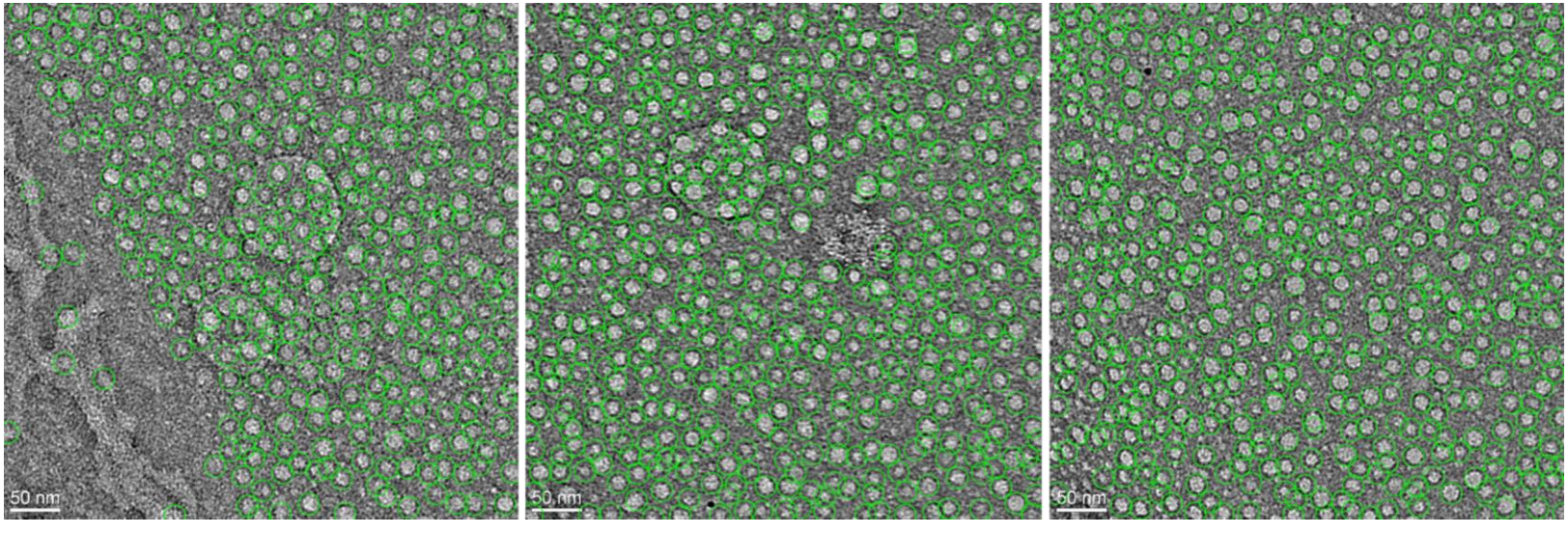




Source TEMs for 2D and 3D Classification



Analyzed Particles



1109 particles

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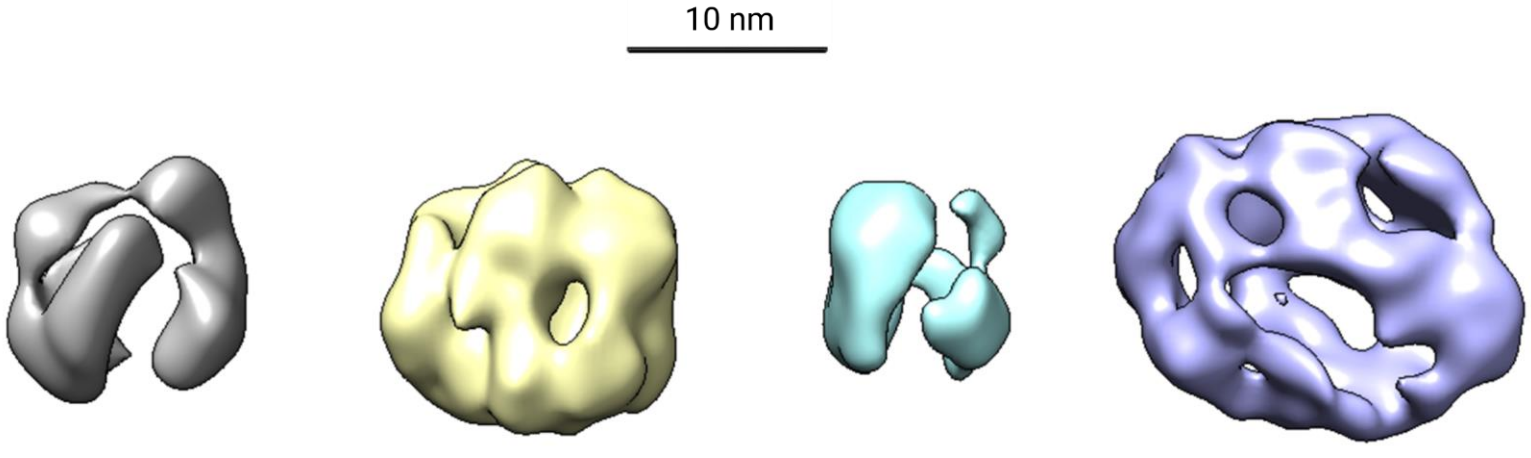
3D Classification



10 nm | 14 nm | 8 nm | 18 nm

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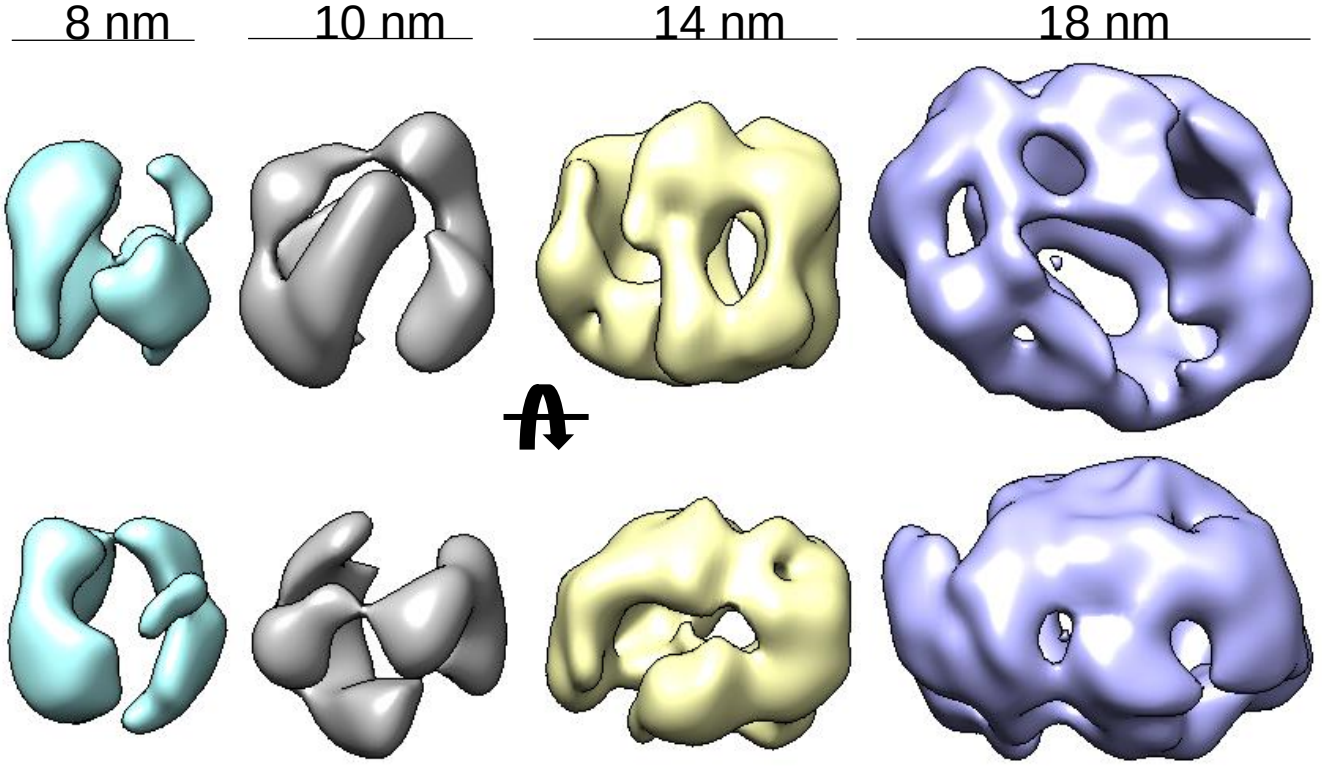
Ab initio 3D Classification



Particles: 64
Threshold: 1.07-1.3
Vol: 99-187 nm3
Est. Mass: 80-152 kDa

Particles: 70
Threshold: 0.866-1.02
Vol.: 269-342 nm3
Est. Mass: 171-277 kDa

Particles: 230
Threshold: 0.579-0.808
Vol: 458-670 nm3
Est. Mass: 371-543 kDa

Particles: 470
Threshold: 0.536-0.833
Vol: 690-1270 nm3
Est. Mass: 558-1028 kDa