Apolipoprotein E: From Structure to Alzheimer's Disease

GLADSTONE INSTITUTE OF NEUROLOGICAL DISEASE

Impact of ApoE Isoforms on AD

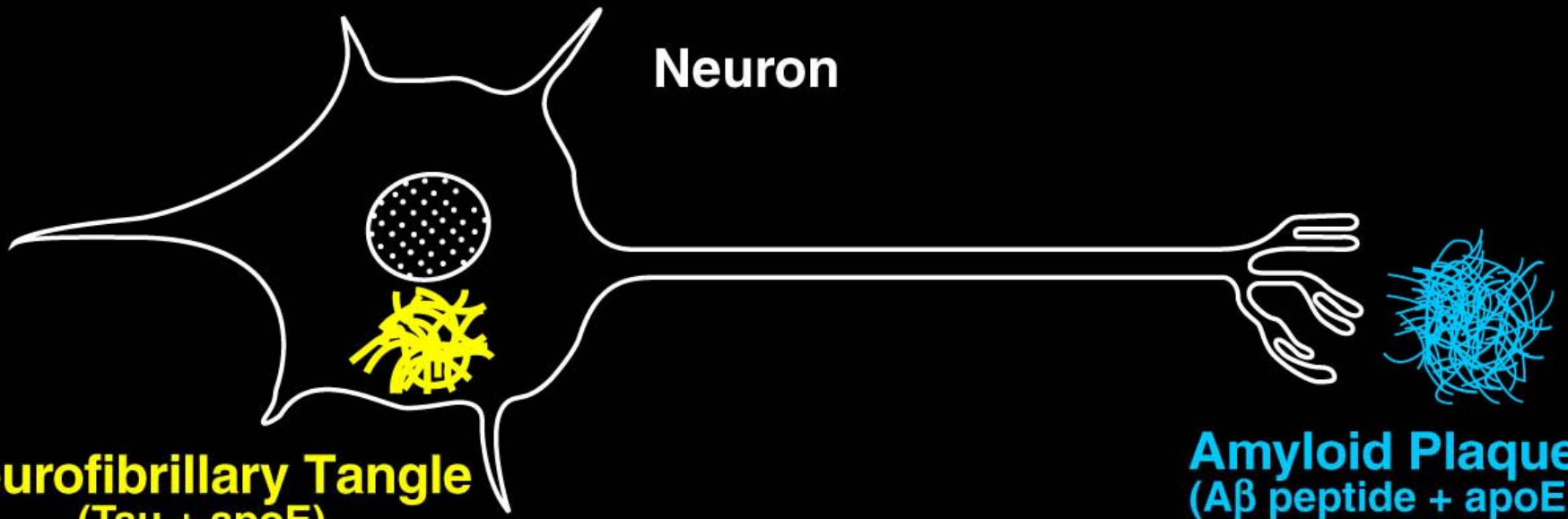
Isoform-specific effects

- Risk: ApoE4 > ApoE3 > ApoE2
- Age of onset: two ε4 - 68 y/o
  one ε4 - 75 y/o
  no ε4 - 84 y/o
- ApoE4 is associated with
  ~ 50% of AD

ApoE: Relationship of Structure to Function

ApoE4:	Arg	Arg
ApoE3:	Cys	Arg
ApoE2:	Cys	Cys

ApoE Is Associated with Tangles and Plaques



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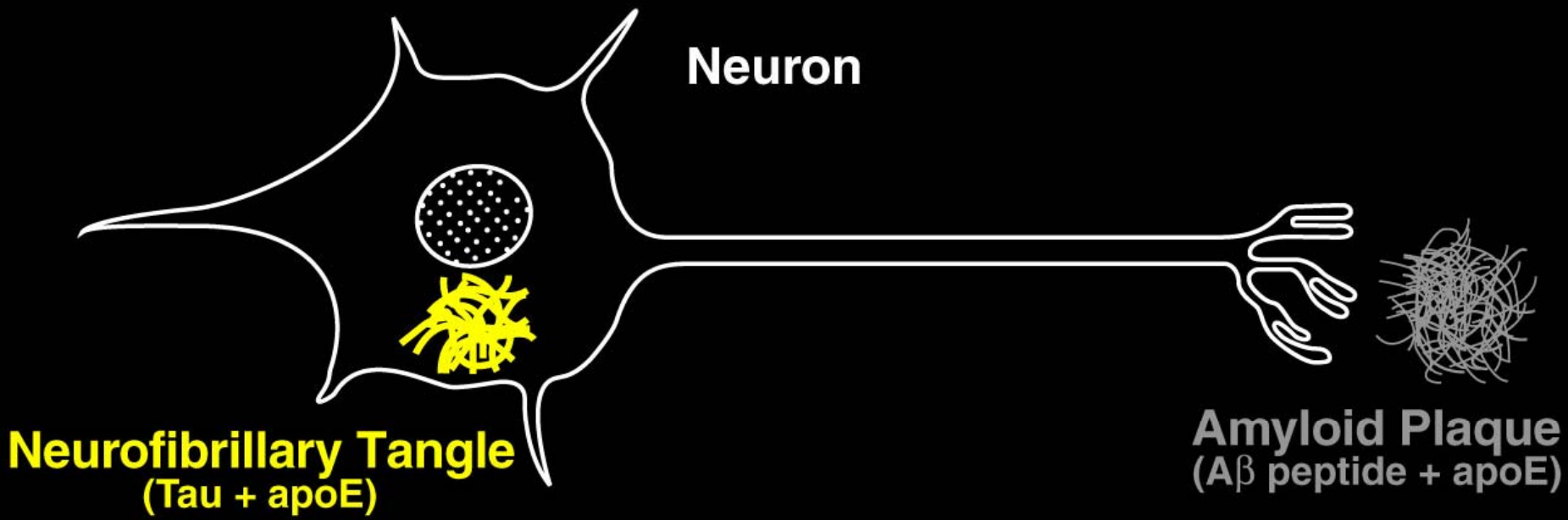

- Isoform-specific binding to tau (apoE3 > apoE4)
- ApoE4 increases tau phosphorylation

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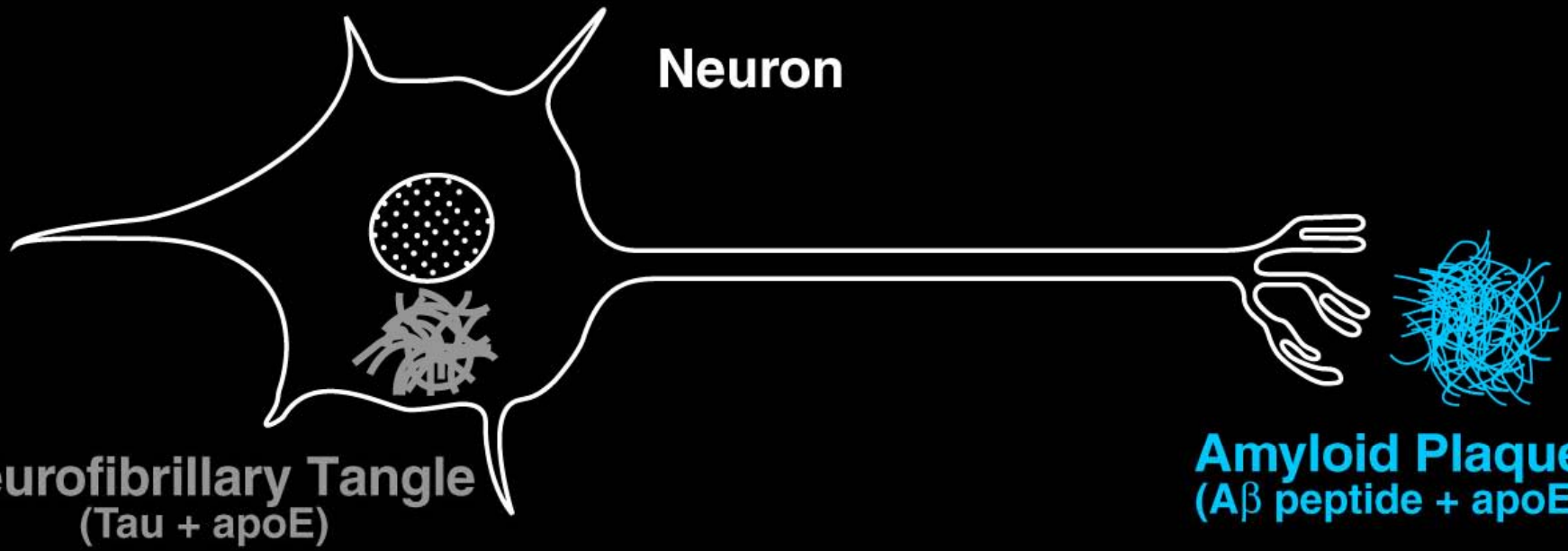


- Isoform-specific binding to tau (apoE3 > apoE4)
- ApoE4 increases tau phosphorylation

- Isoform-specific binding to Aβ dependent on source - suggesting a role in clearance
- ApoE4 promotes Aβ fibers

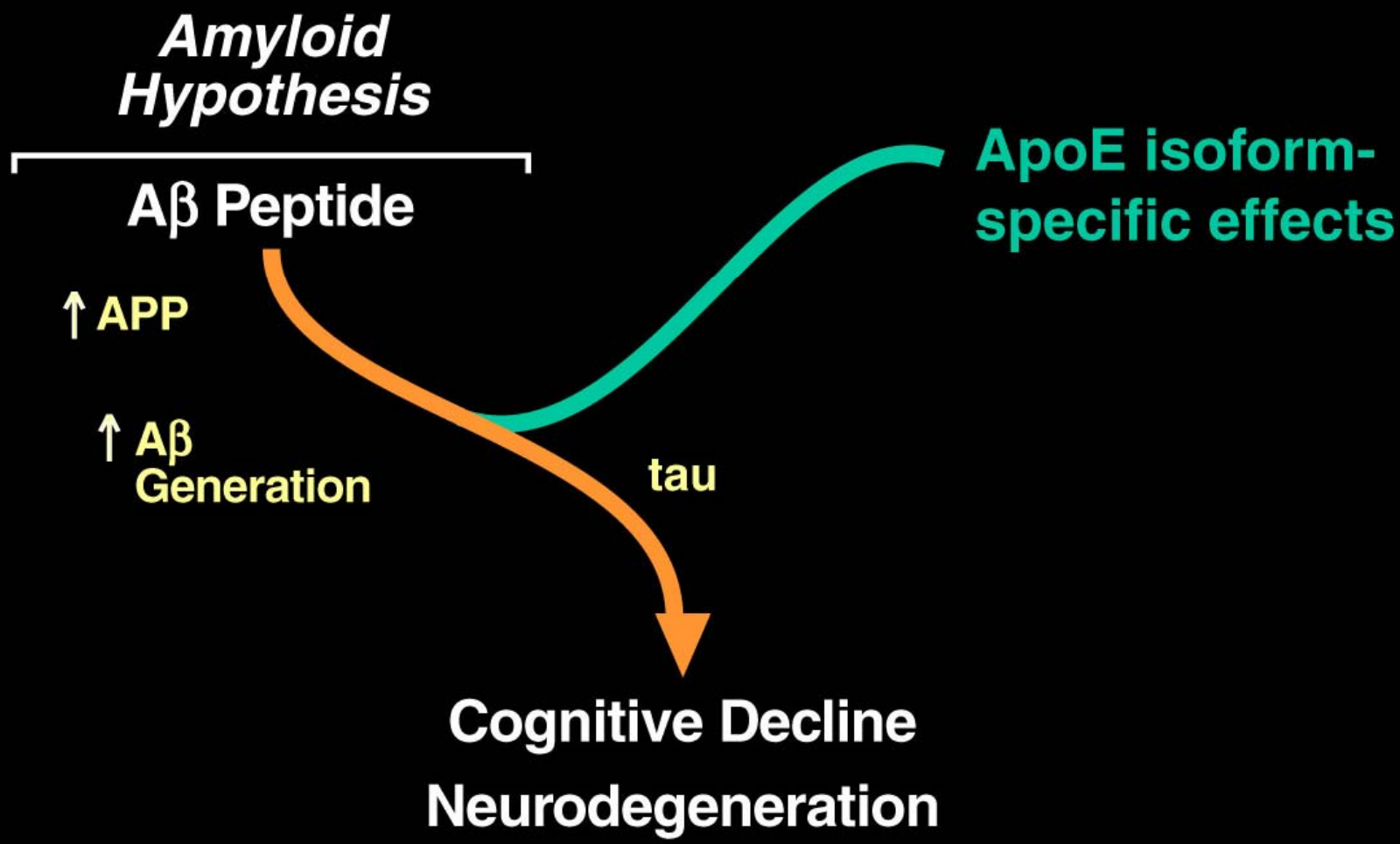
Human ApoE Transgenic Models
(mouse apoE-null)

Relative to apoE3:

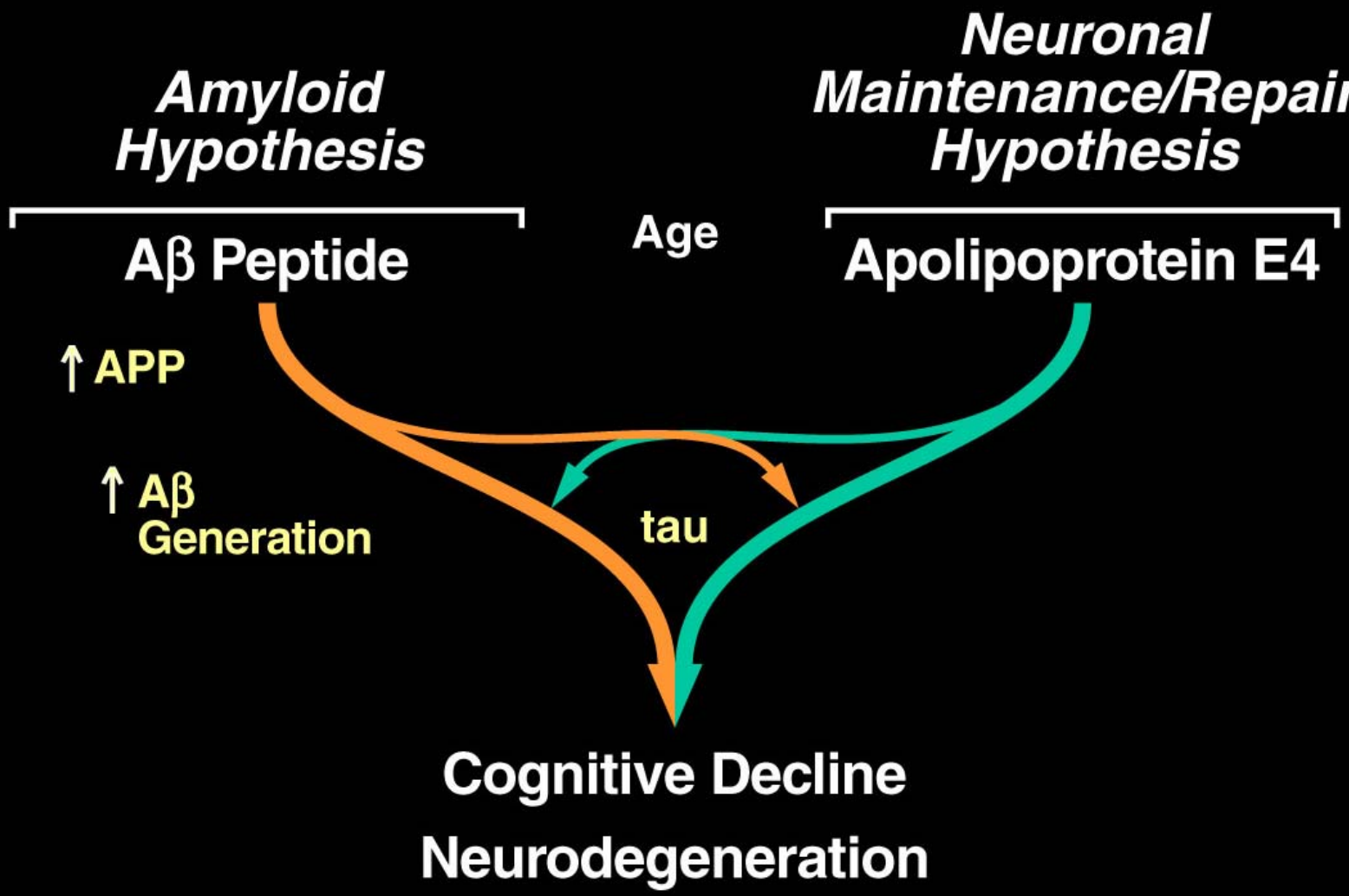
AD-like features

- ↑ plaques with hAPP/E4
- ↓ presynaptic terminals with E4 with or without hAPP
- E4 neuronal expression ↑ P-tau, ubiquitin-containing inclusions, and gliosis
- E4 impairment with spatial learning and memory

ApoE Isoform-specific Interactions with Aβ Peptide Causing Cognitive Decline and Neurodegeneration



Interaction of Multiple Factors through Various Pathways Causing Cognitive Decline and Neurodegeneration



Major Questions and Challenges

ApoE4
ApoE3
in vitro studies

in vivo

1) What are the mechanisms involved?

2) How to move from mechanisms to therapeutics?

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How can structure help?

ApoE: Relationship of Structure to Function

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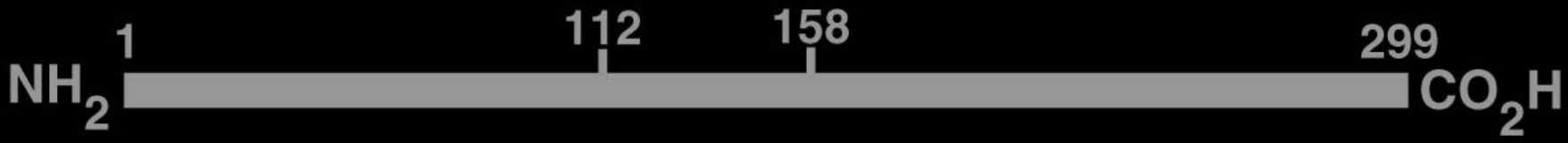

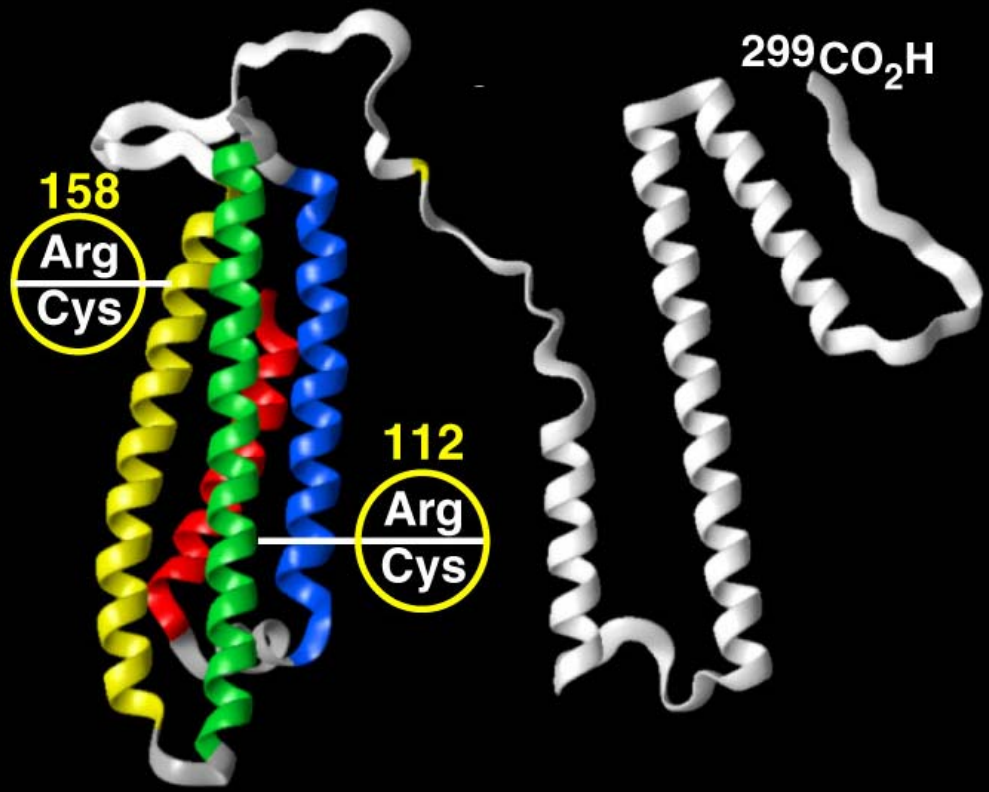

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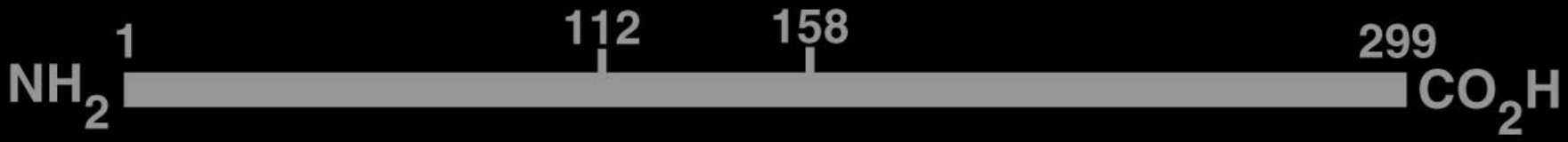

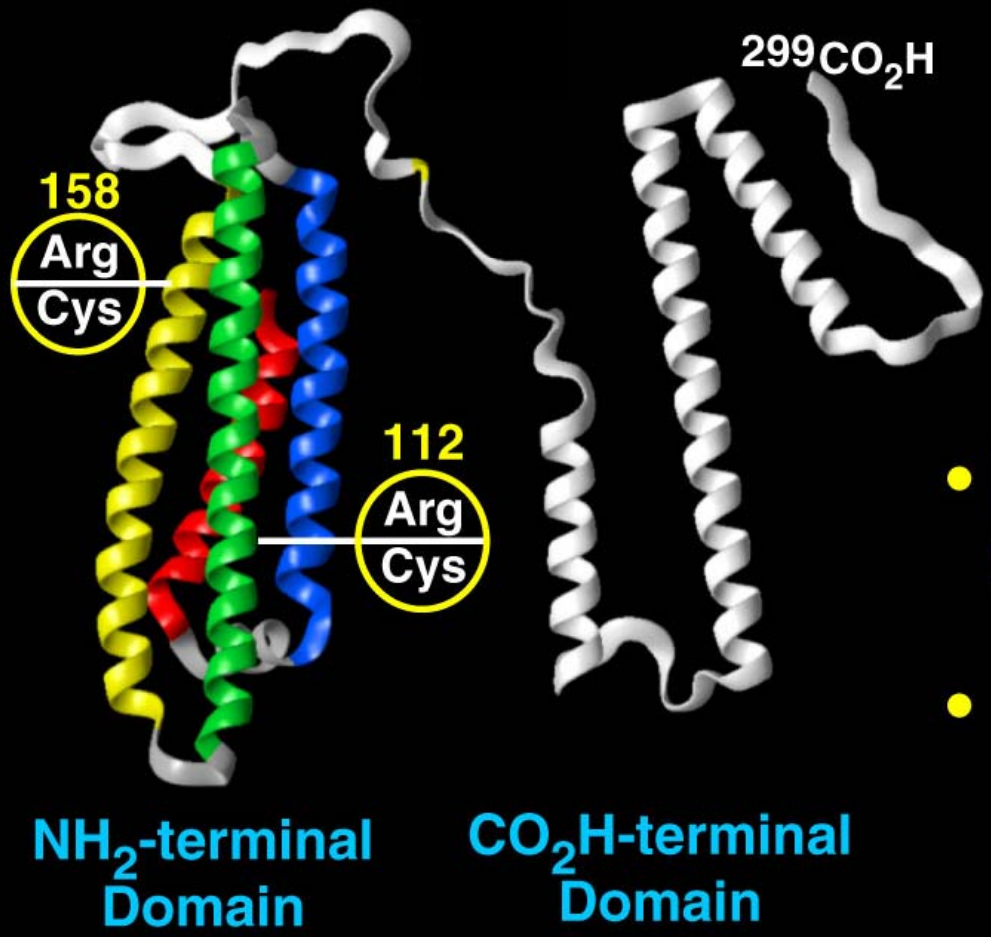

- Protein Stability (Molten Globule)
- Domain Interaction

Protein Folding and Stability

Protein misfolding emerging importance in neurodegenerative diseases

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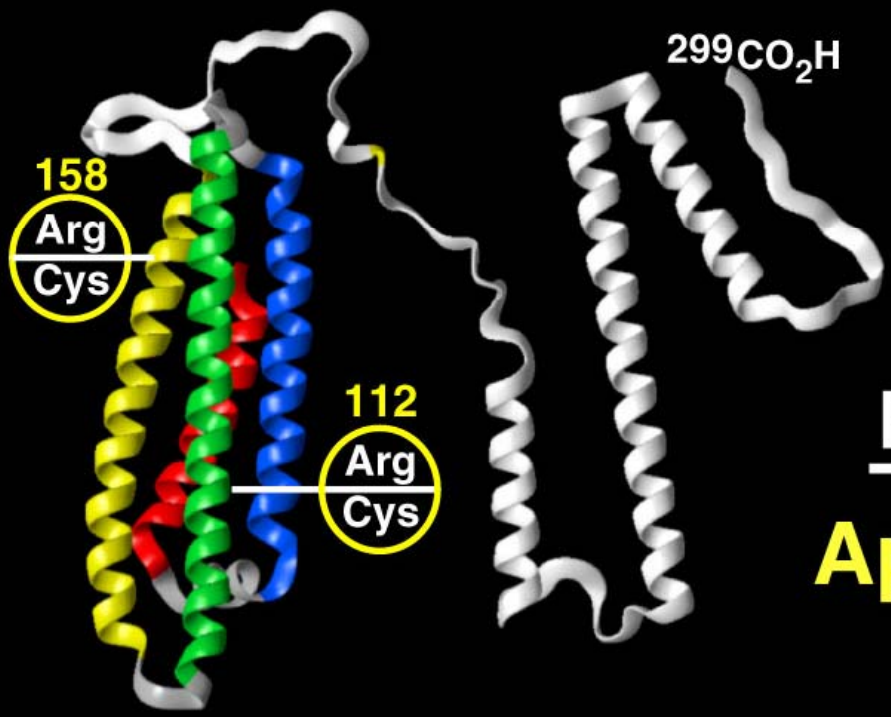
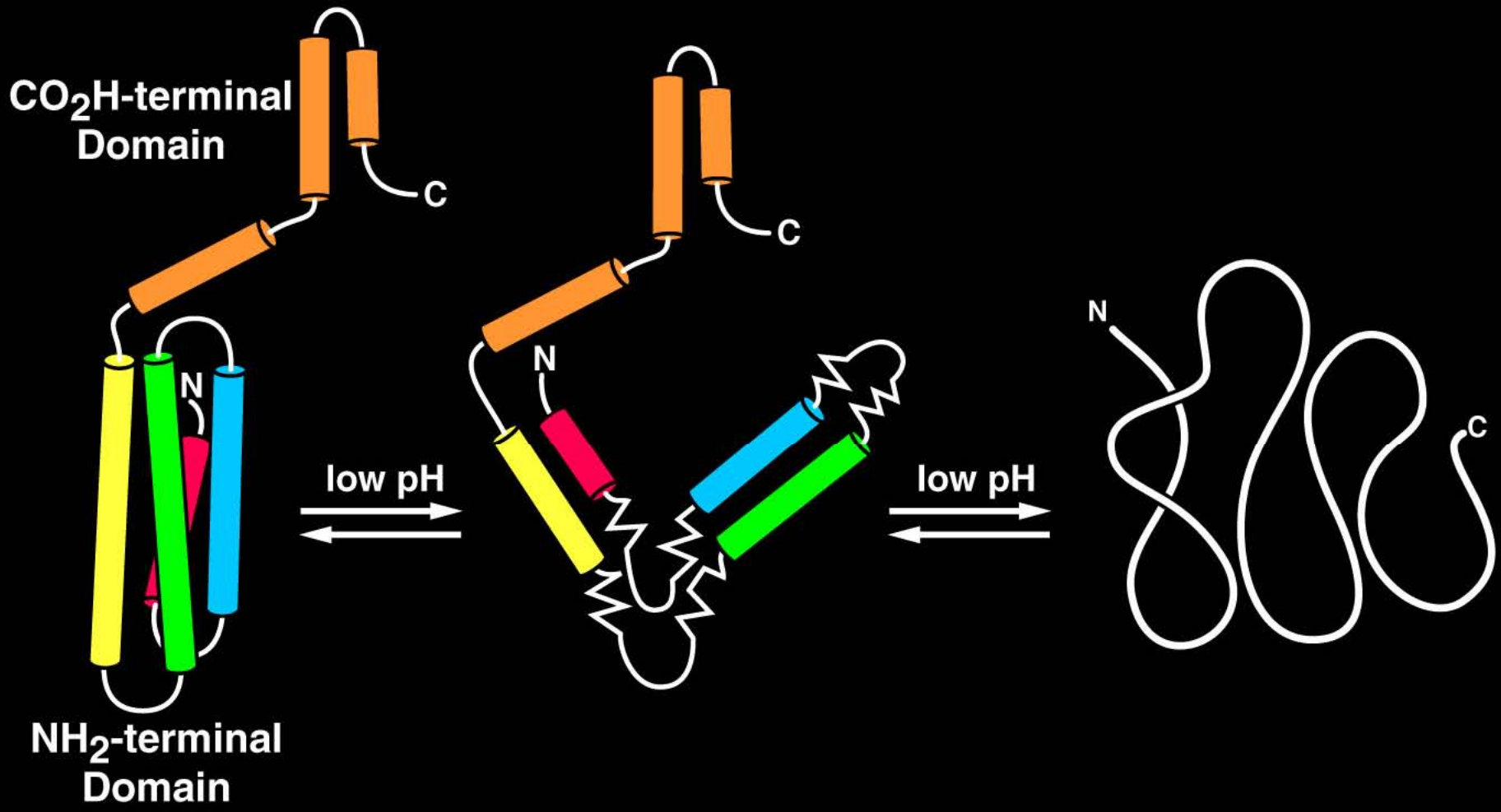
Protein misfolding emerging importance in neurodegenerative diseases



Relative ApoE Stabilities

ApoE4 < ApoE3 < ApoE2

Unfolding/Stability of ApoE



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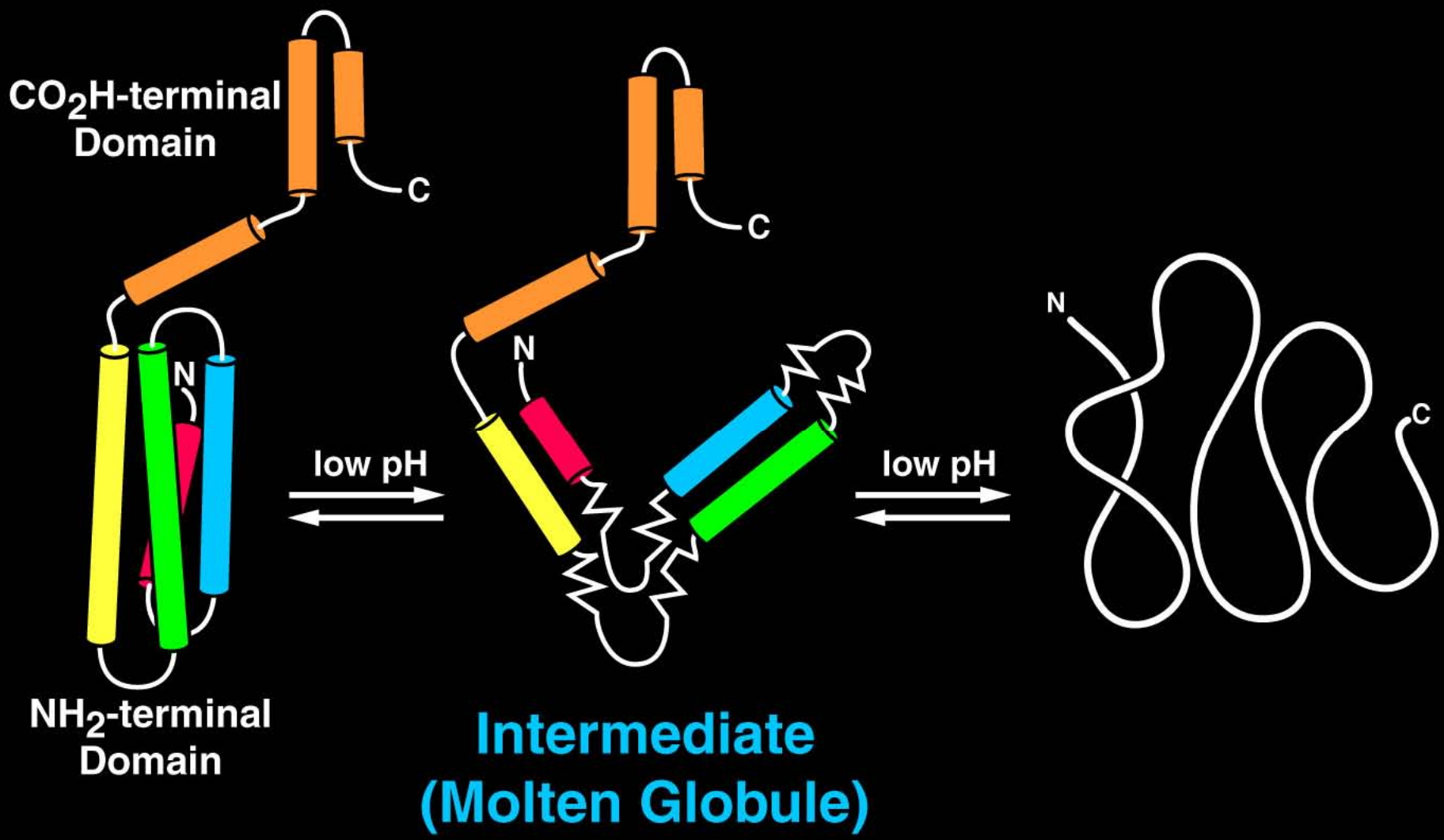

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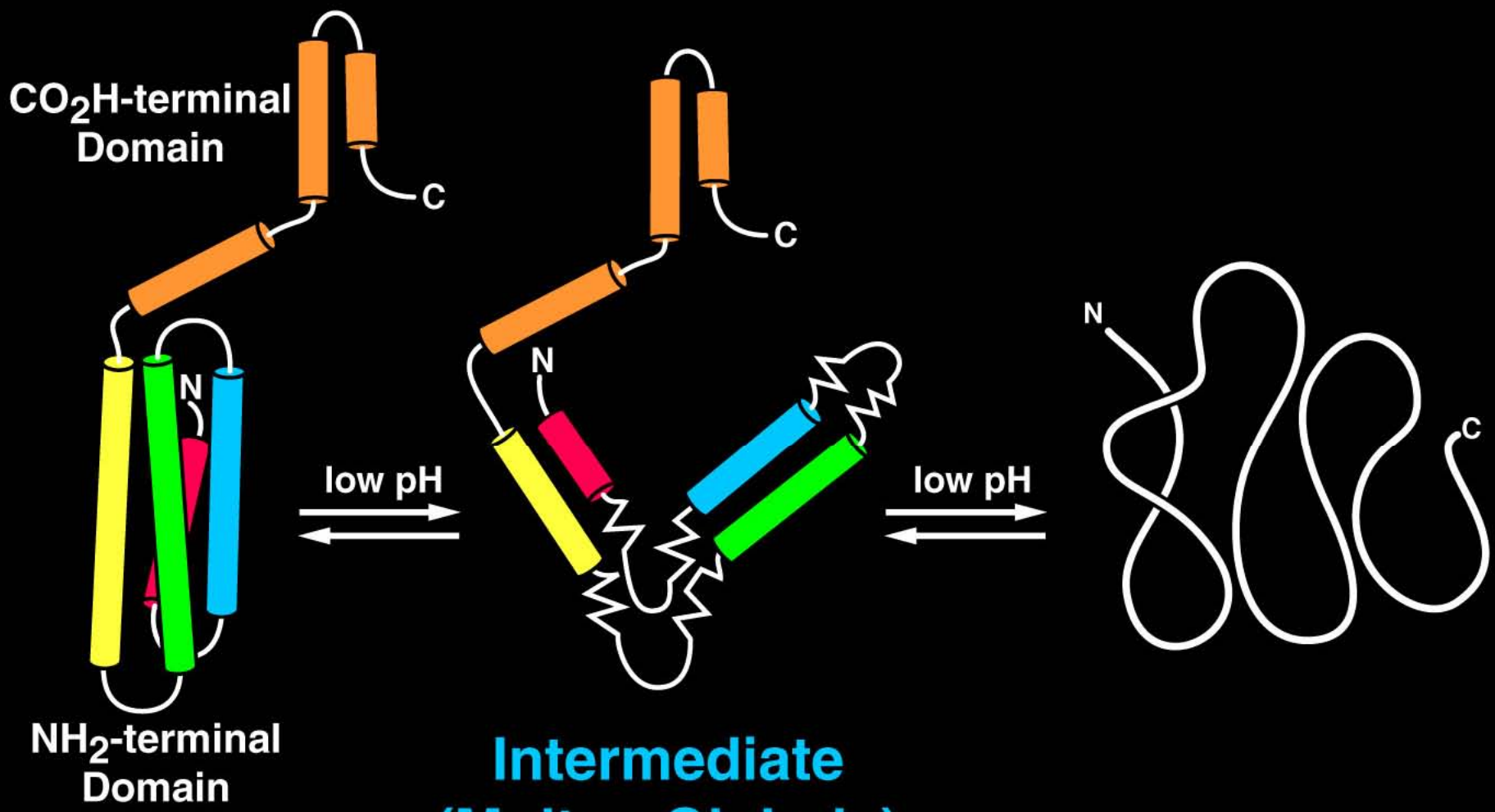
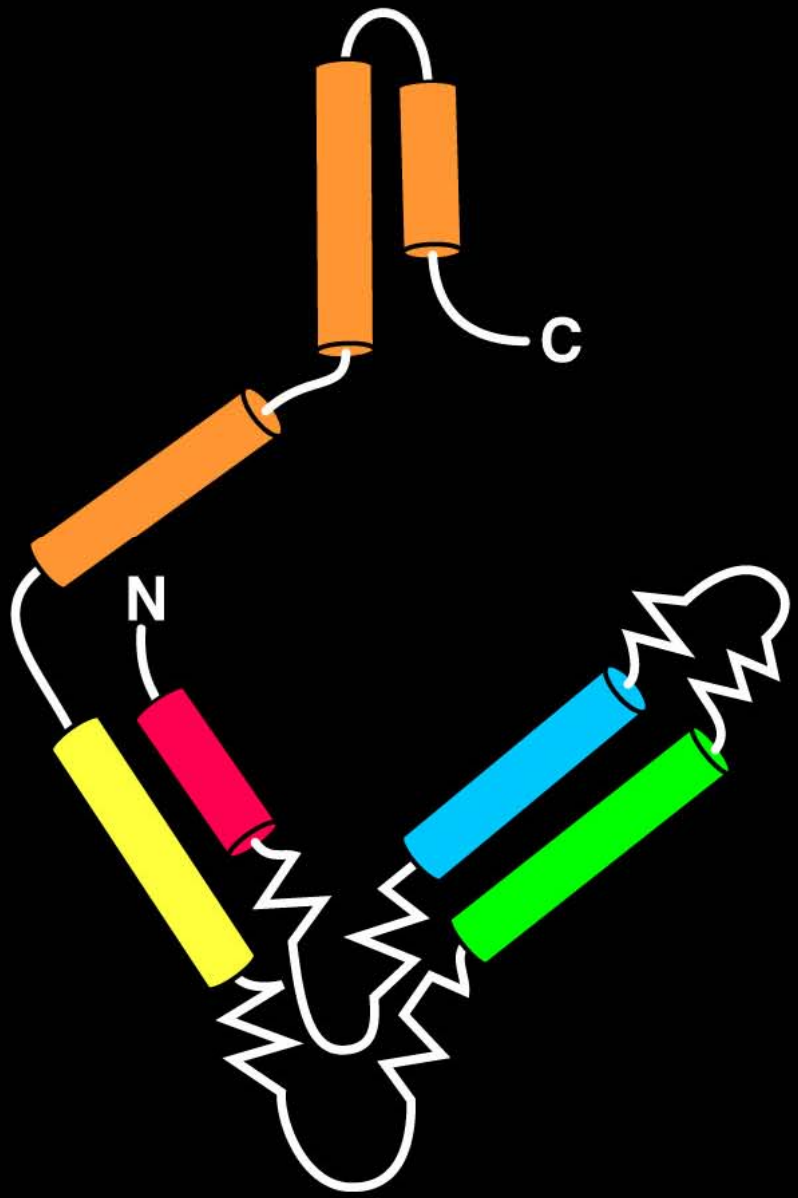


ApoE4 > ApoE3 > ApoE2

Implications of Molten Globule Formation



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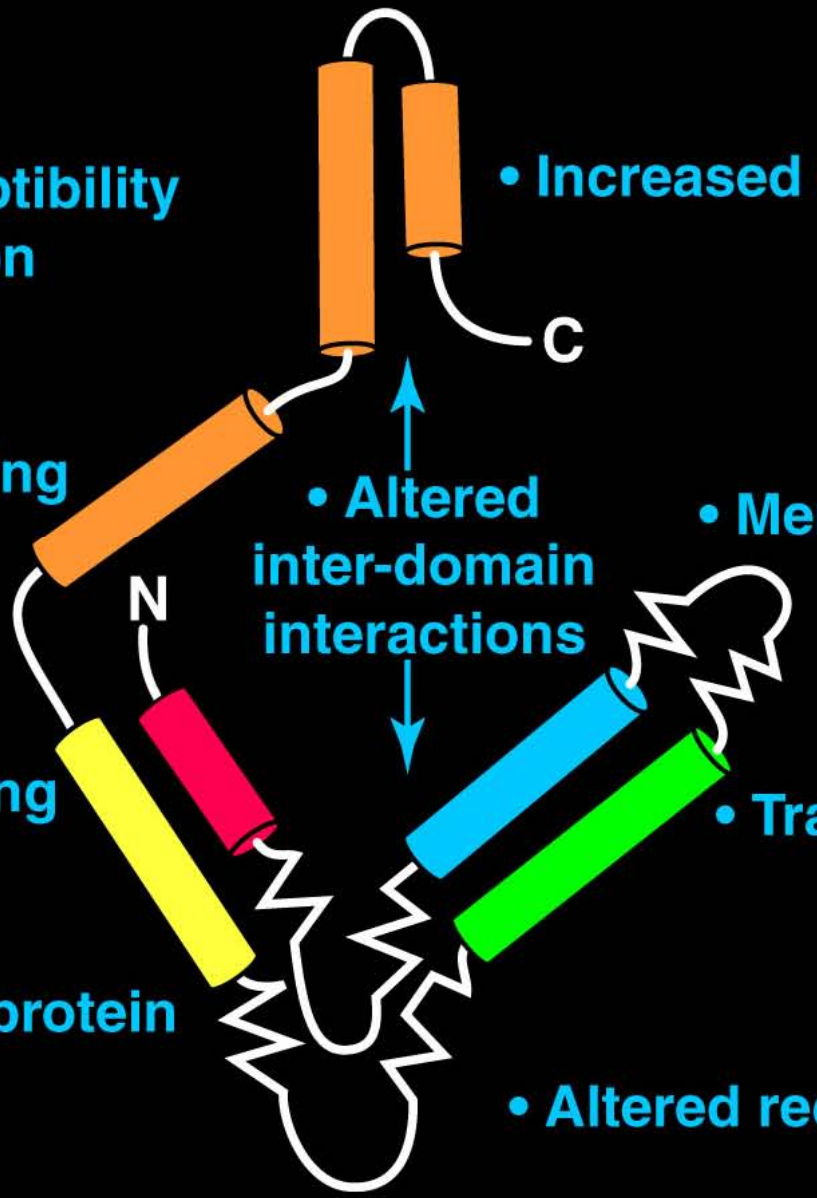
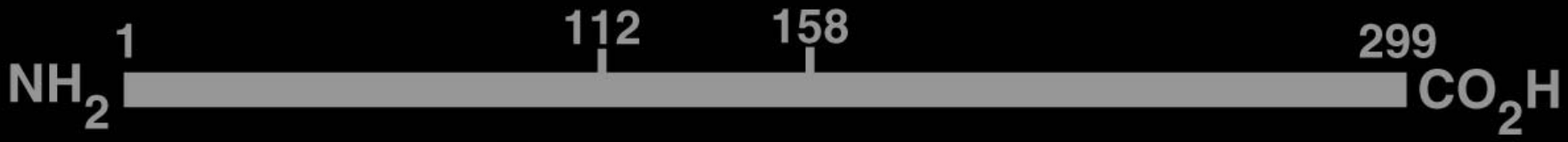
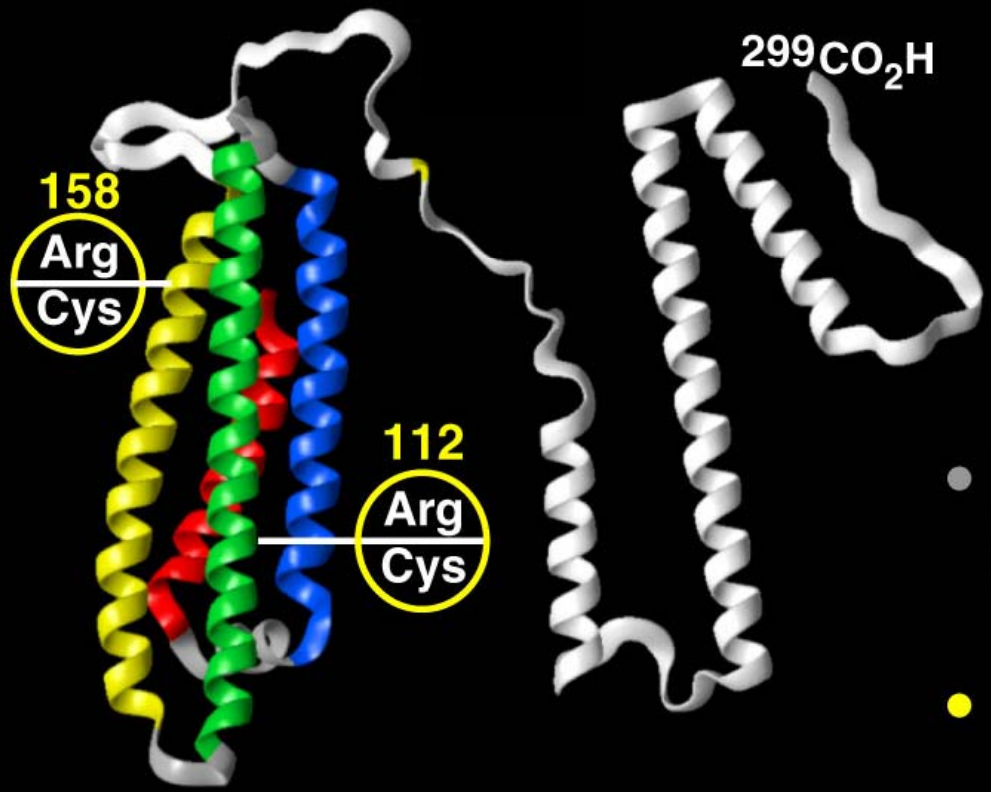


- Increased susceptibility to degredation
- Increased membrane binding
- Altered cell signaling
- Altered inter-domain interactions
- Membrane disruption
- Altered lipid binding preferences
- Translocation across membranes
- Abnormal protein:protein interactions
- Altered receptor interactions

ApoE: Relationship of Structure to Function

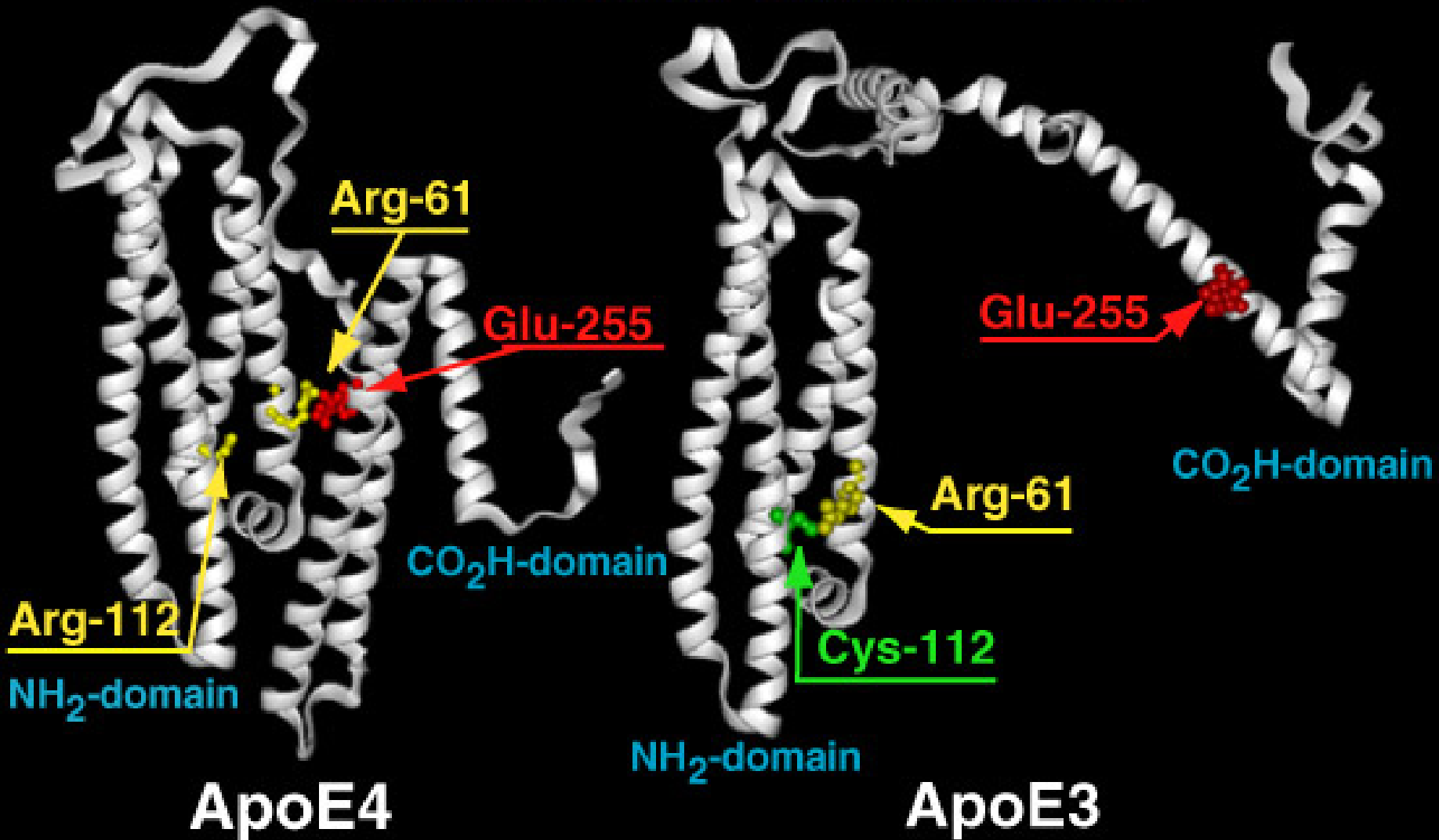




- Protein Stability (Molten Globule)
- **Domain Interaction**

ApoE4 Domain Interaction

Effect of Position 112 on Structure



Human ApoE Transgenic Models
(mouse apoE-null)

ApoE4 effects:

Protein Stability (Molten Globule)

Domain Interaction

“Designer” Mouse Model Approach

Protein Stability (Molten Globule)

Domain Interaction

Mouse model for specific apoE4 property

"Designer" Mouse Model Approach

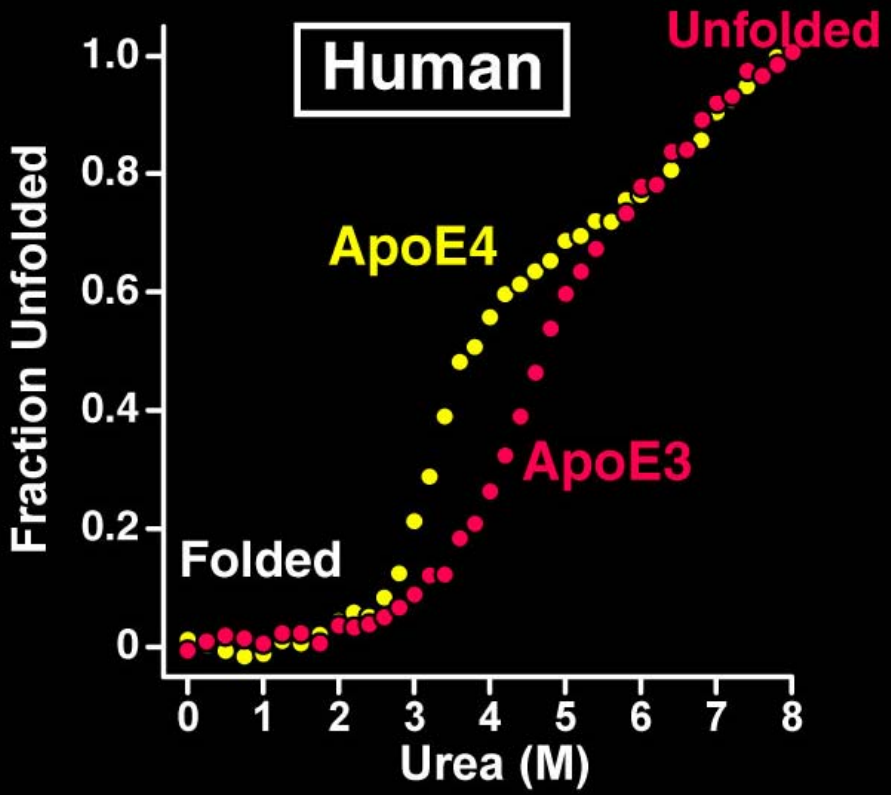
Protein Stability (Molten Globule)

Domain Interaction

"Humanize"

Mouse ApoE

Mouse model for specific apoE4 property



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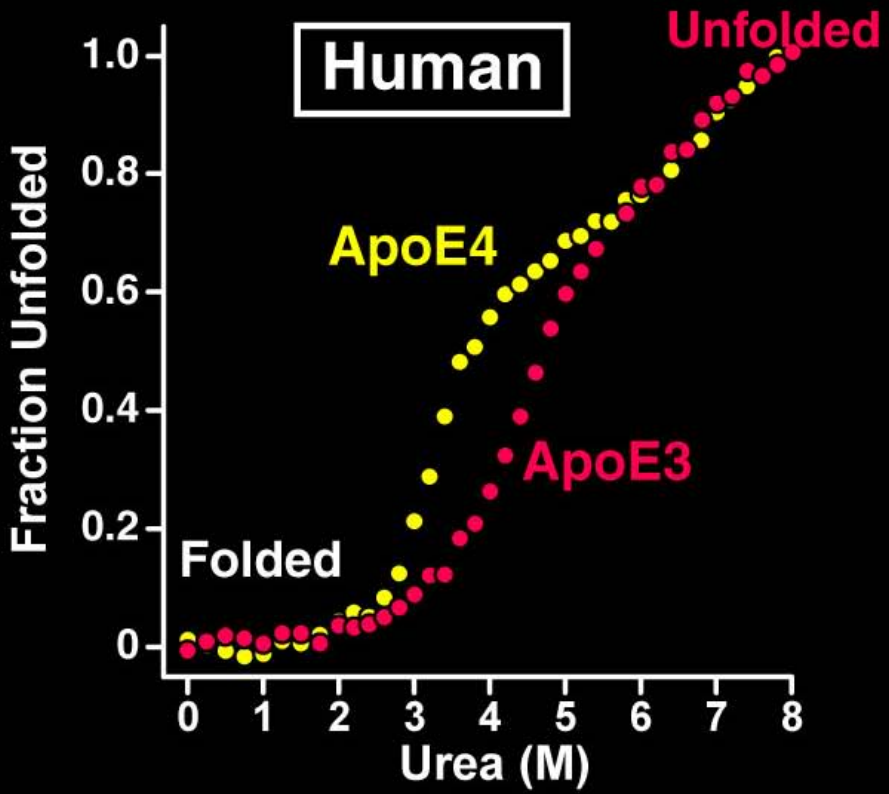
Protein Stability (Molten Globule)

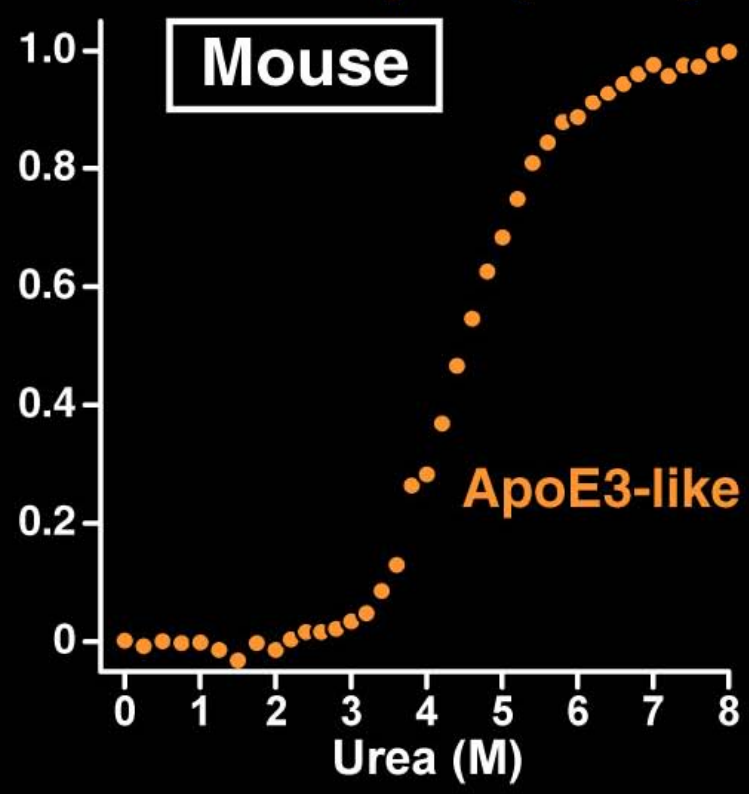
Domain Interaction

"Humanize"

Mouse ApoE

Mouse model for specific apoE4 property





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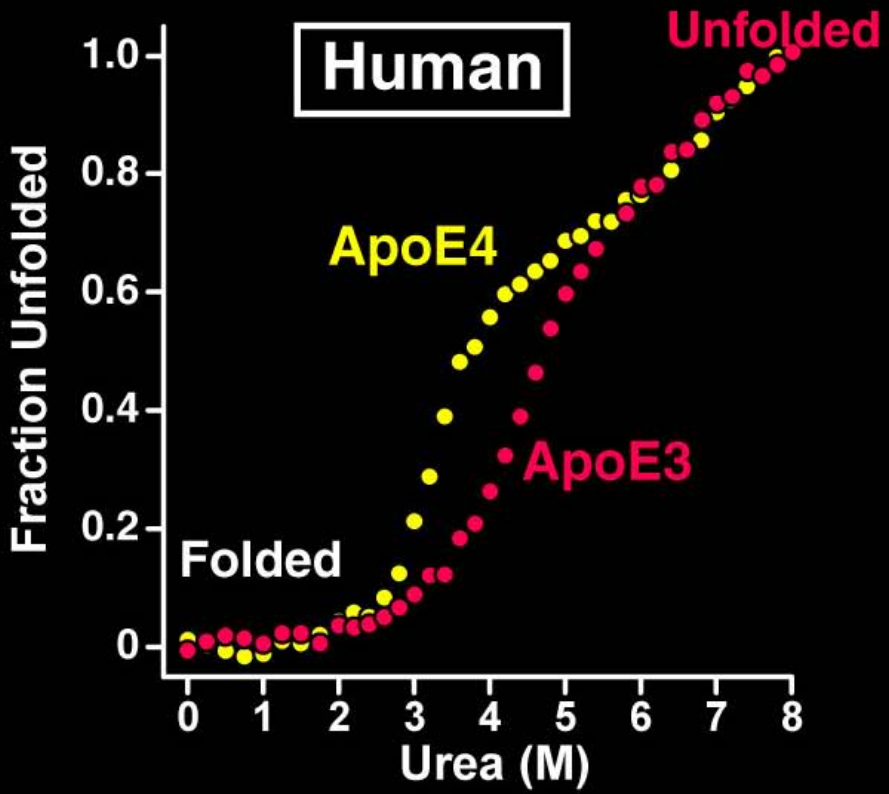

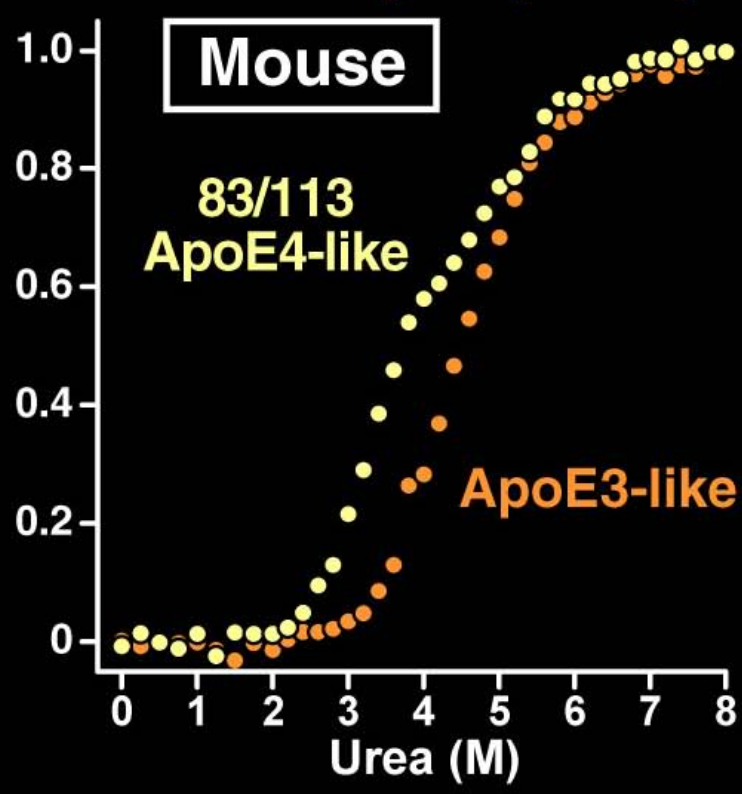

“Designer” Mouse Model Approach

Protein Stability
(Molten Globule)

Domain Interaction

“Humanize”

Mouse ApoE

Mouse model for specific apoE4 property

ApoE4 Domain Interaction Mouse Model

	61	112	255	Domain interaction
Human ApoE3	Arg	Cys	Glu	No
Human ApoE4	Arg	Arg	Glu	Yes
Mouse wt ApoE	Thr	Arg	Glu	
Mouse Arg-61	Arg	Arg	Glu	

ApoE4 Domain Interaction Mouse Model

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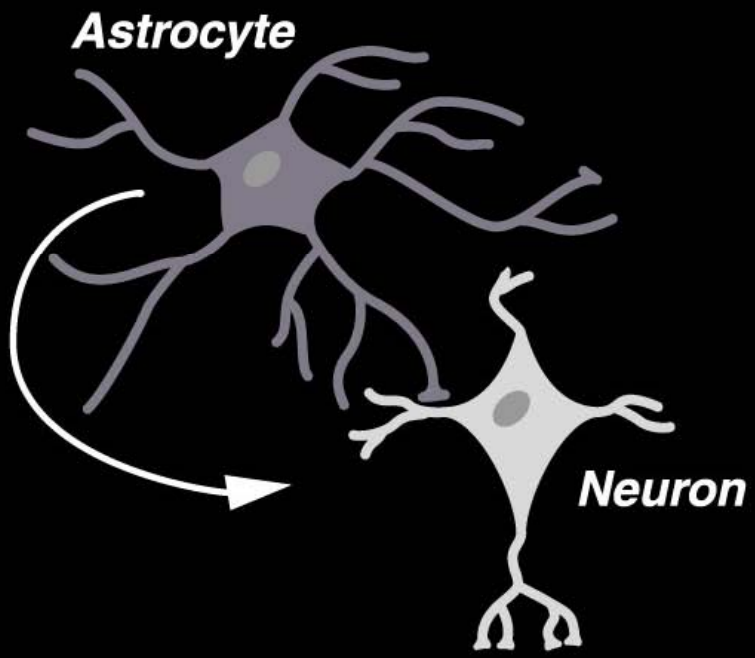
Human ApoE3	Arg	Cys	Glu	No
Human ApoE4	Arg	Arg	Glu	Yes
Mouse wt ApoE	Thr	Arg	Glu	No
Mouse Arg-61	Arg	Arg	Glu	Yes

Used gene-targeting to replace Thr codon in mouse *Apoe* with Arg codon to generate model of Domain Interaction

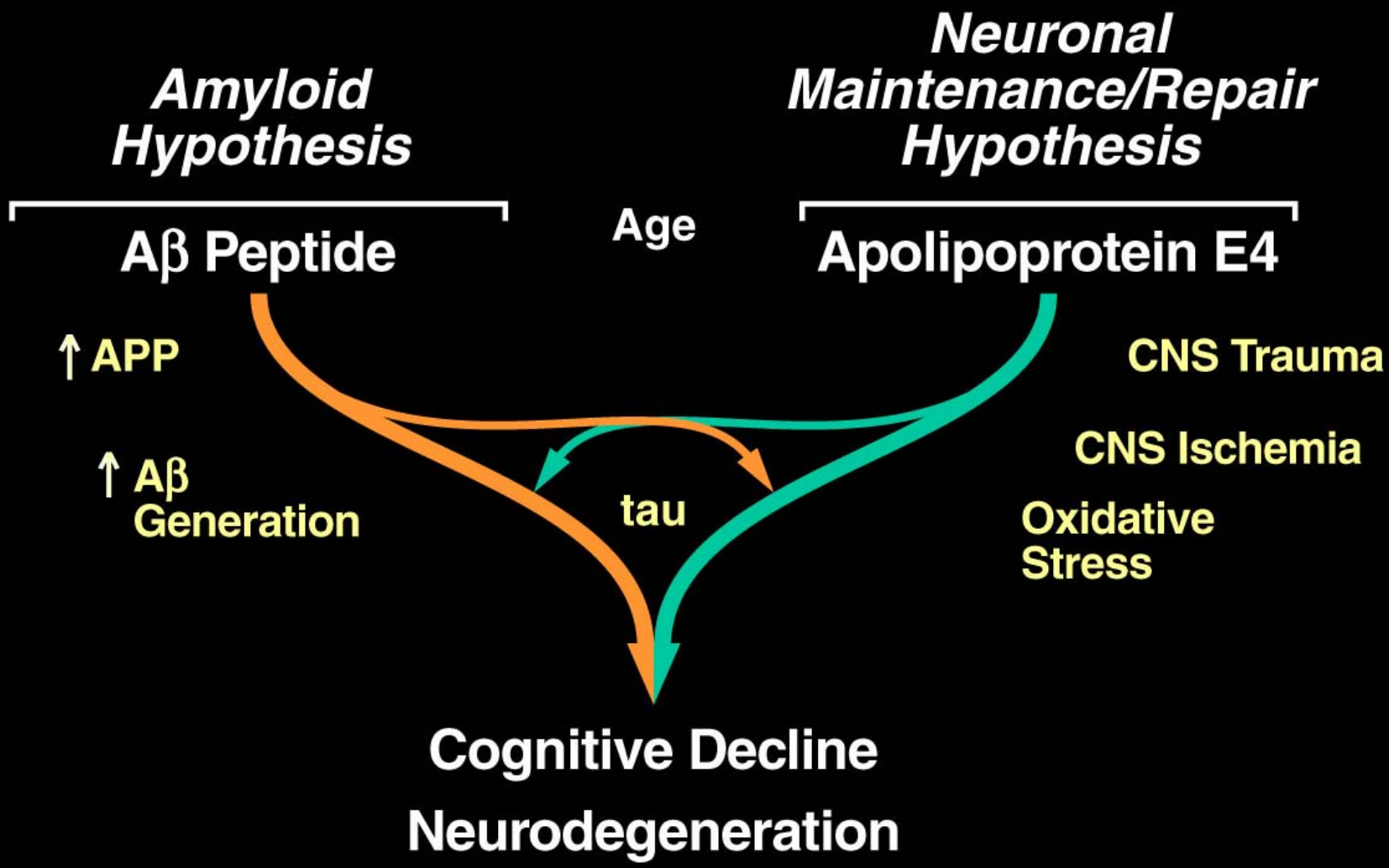
ApoE4 Designer Mouse Models

1) Arg-61 Domain Interaction Mice
2) 83/113 Molten Globule Mice

- lipid transport
- neuronal repair



- Aβ metabolism
- fragmentation
- behavior
- neurodegeneration

To determine relative contribution of domain interaction and molten globule formation to known apoE4 effects in the brain

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