Molecular intervention into amyloid formation

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Protein misfolding diseases

- **Common features** of protein folding diseases
- **Molecular mechanisms** (Alzheimer, Parkinson, polyQ disorders, systemic amyloidosis)
- **Therapeutic strategies** for amyloid diseases (anti-aggregation therapies)

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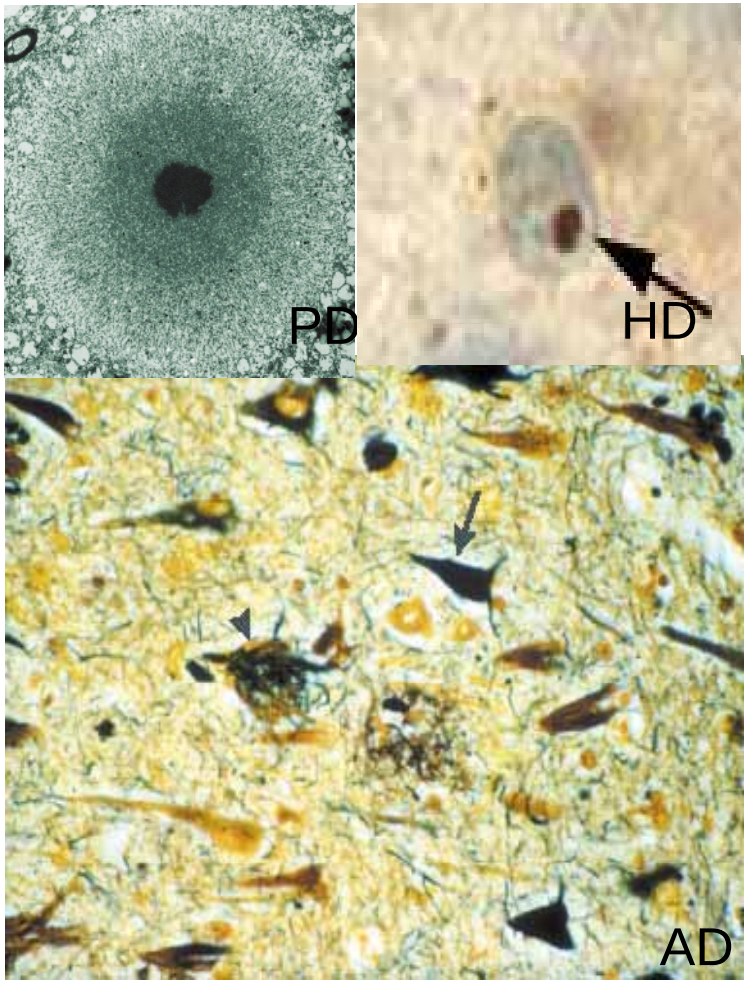
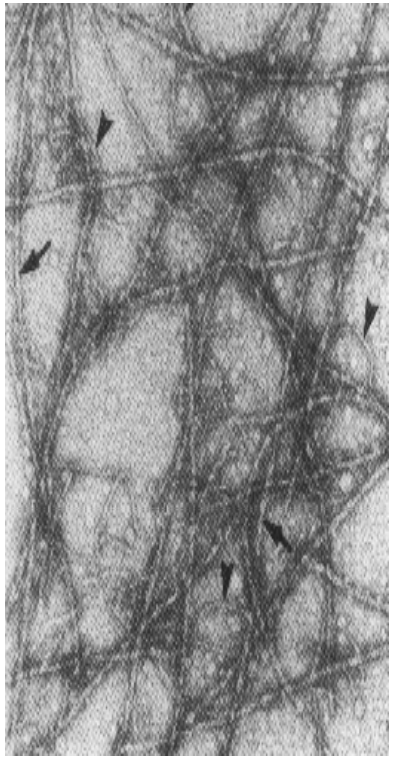
Formation of insoluble protein aggregates is a common feature of amyloid diseases



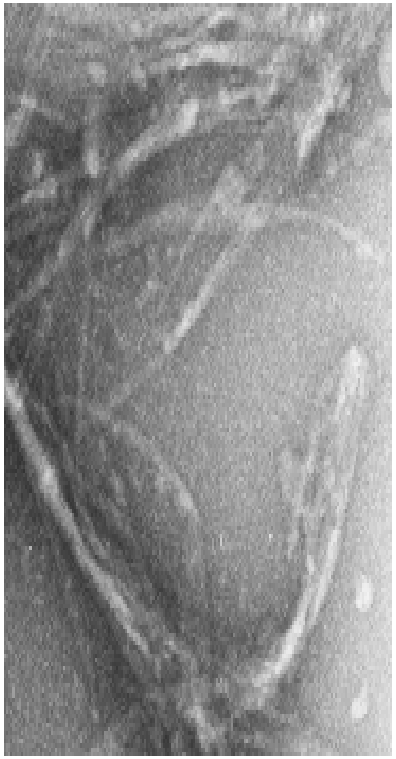
Clinical syndrome	Oligomer/aggregate component
Alzheimer‘s disease	Amyloid-ß (Aß) peptide
Huntington‘s disease	Huntingtin, or huntingtin fragments
Parkinson‘s disease	α - Synuclein
Spongiform encephalopathies	Prion, or prion fragments
Type II diabetes	Fragment of IAPP

Amyloid Fibrillogenesis

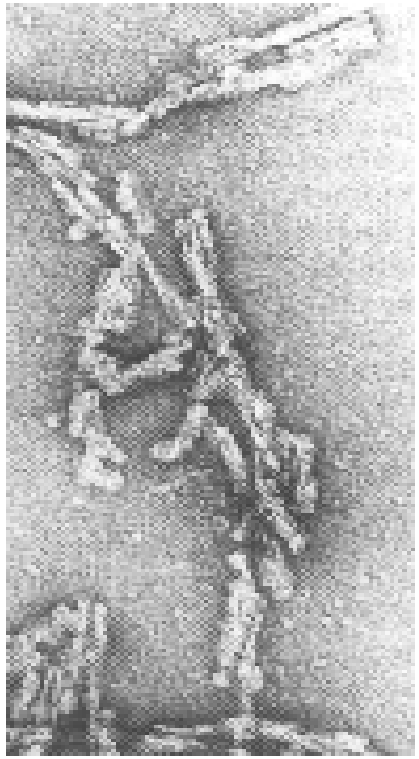
Amyloid-β



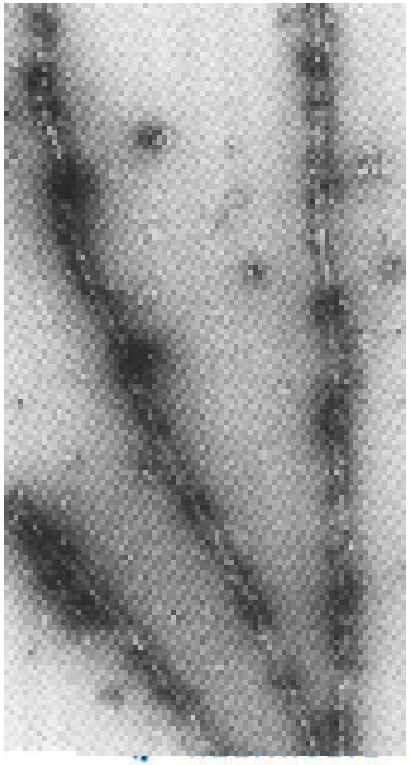
Huntingtin



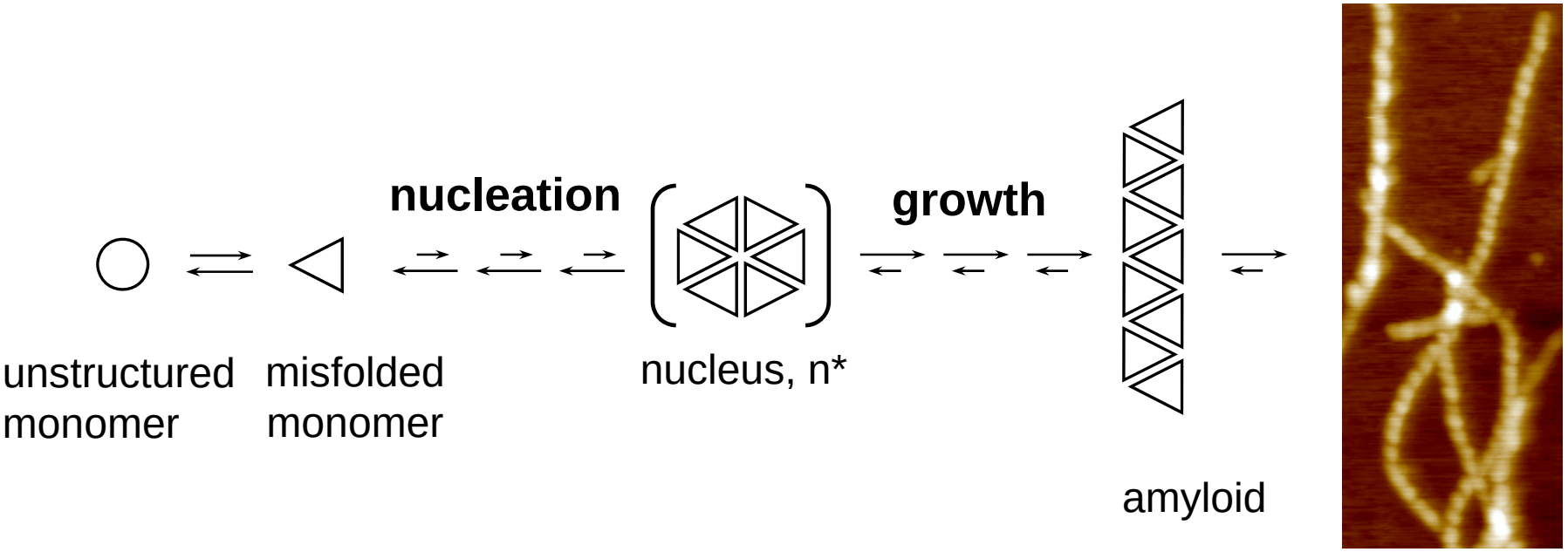
Prion protein



Synuclein



Mechanism of amyloid formation



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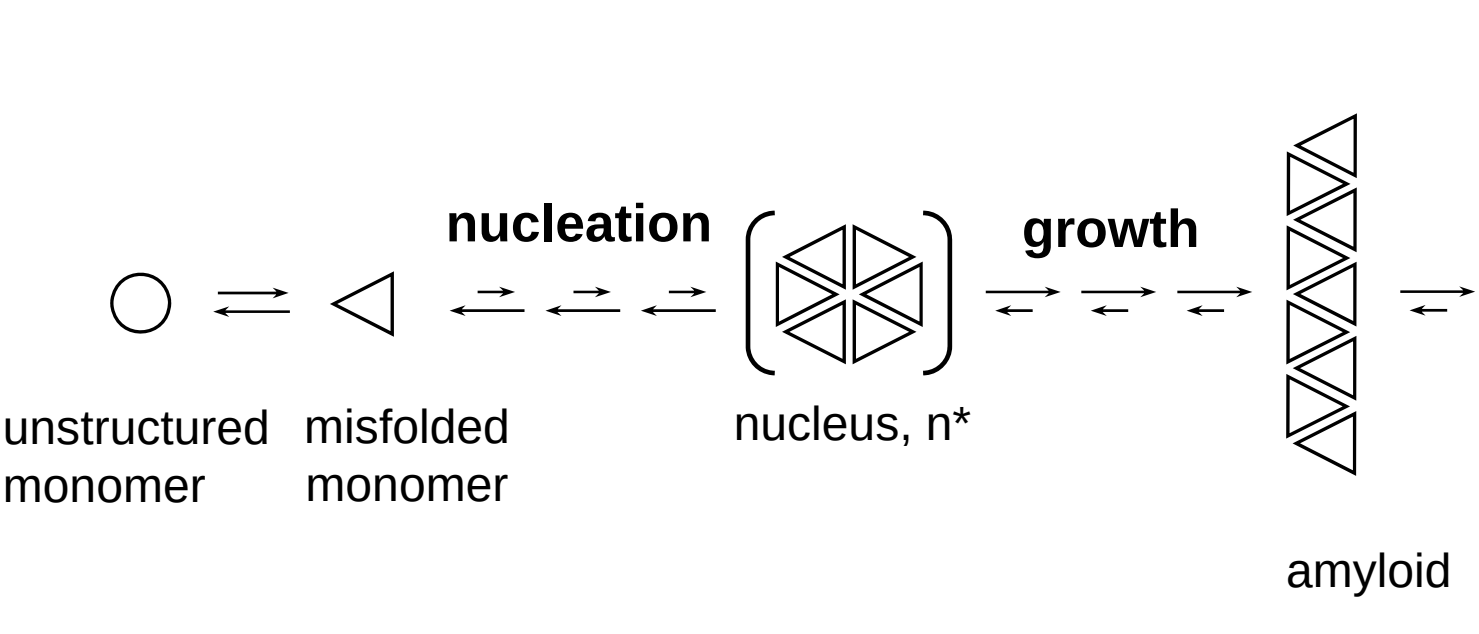

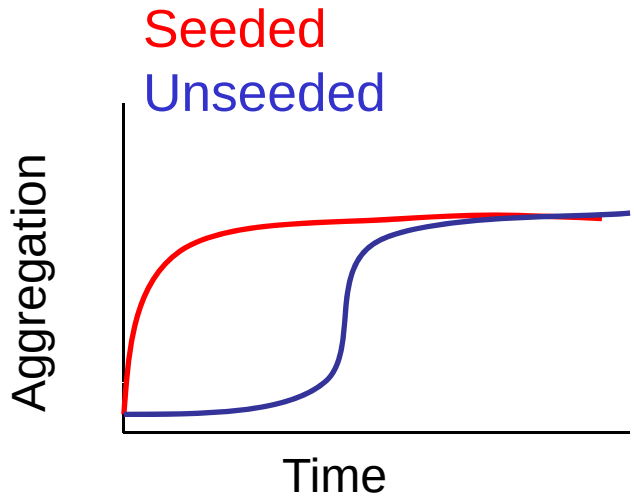

Amyloid markers:

- Dye binding (Thioflavin T, Congo Red)
- Resistance to denaturation

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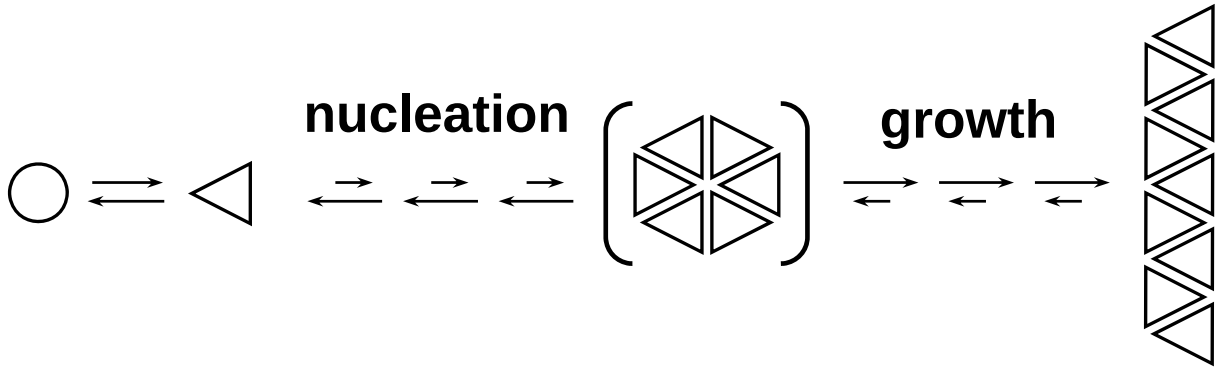
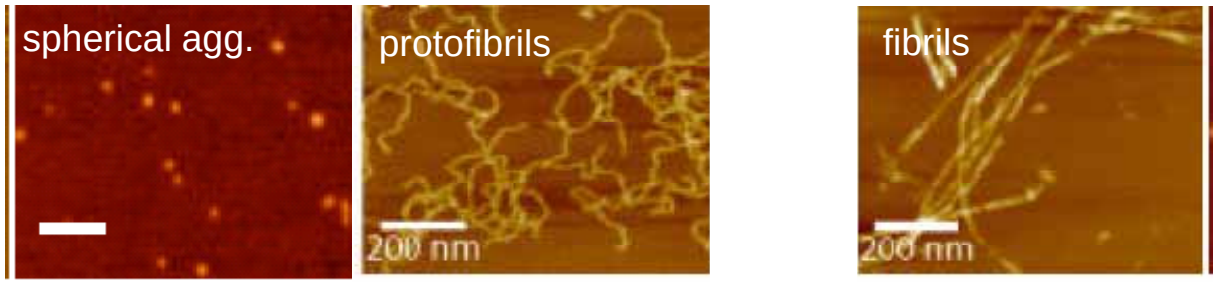
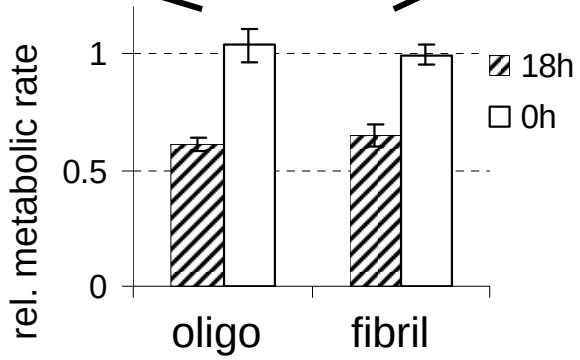
Toxic Aβ amyloid intermediates





Toxicity



Fu, Bieschke & Kelly *JACS* 2005
Bieschke, et al. Biochemistry 2008

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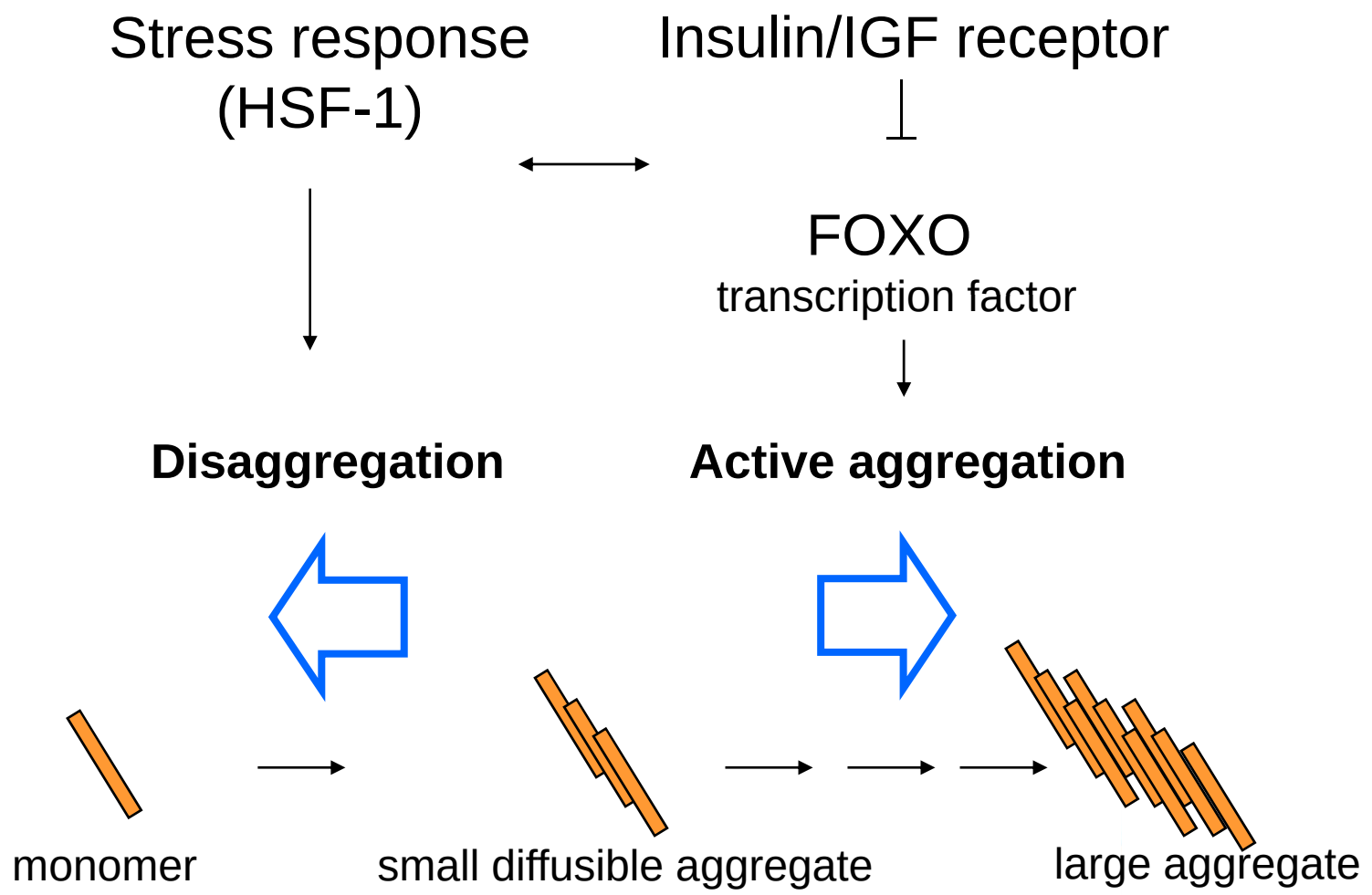
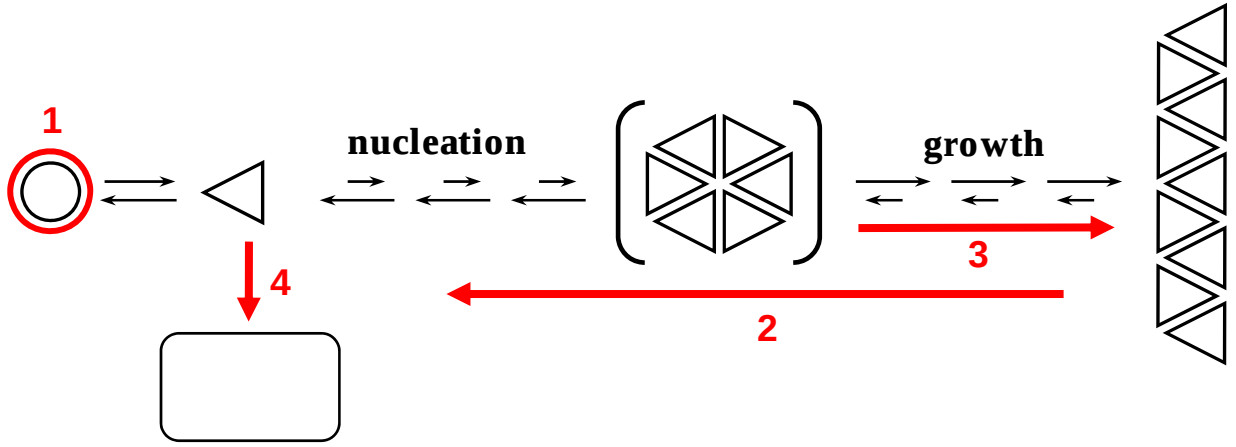
Aging-related insulin and stress response pathways modulate amyloid toxicity

Cohen & Bieschke, Science 2006

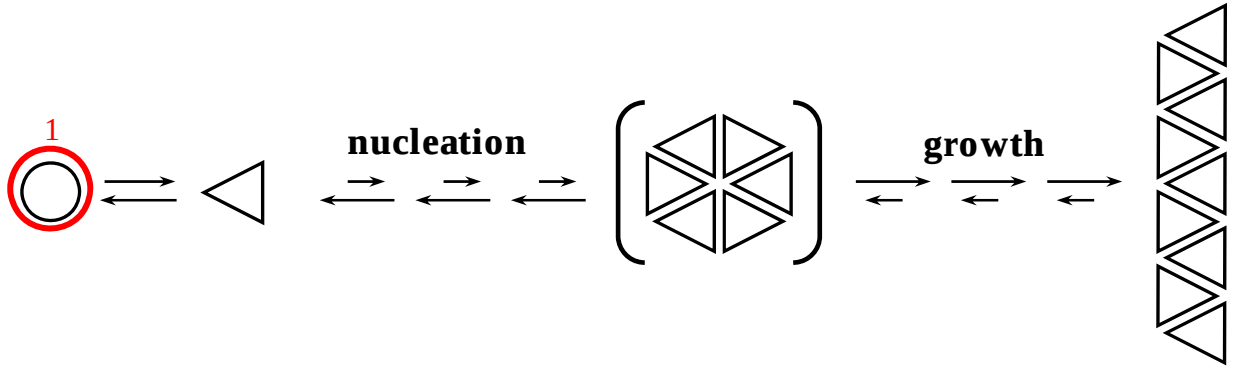


Anti-amyloid intervention strategies



1. Prevent amyloid formation / stabilize monomer
2. Destabilize amyloid: β-sheet breaker, congo red
3. Induce amyloid aggregate fomation (on-pathway)
4. Redirect amyloid aggregate formation (off-pathway)

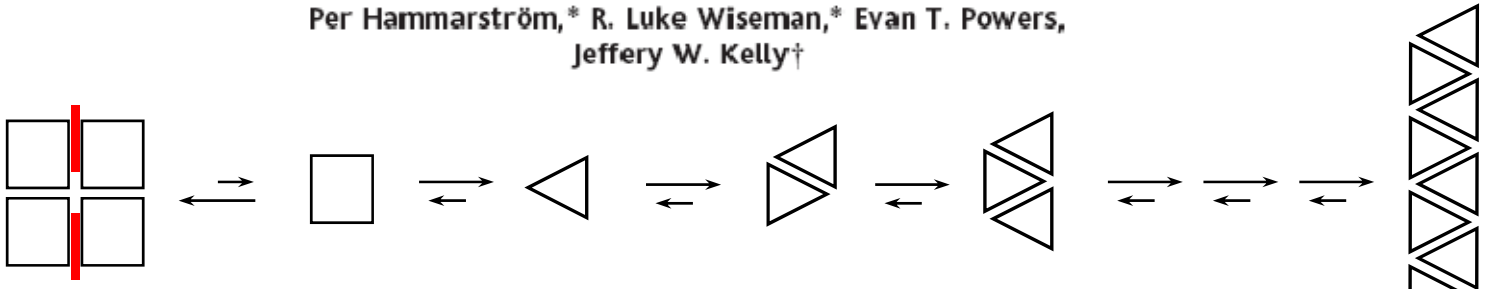
Anti-amyloid intervention strategies



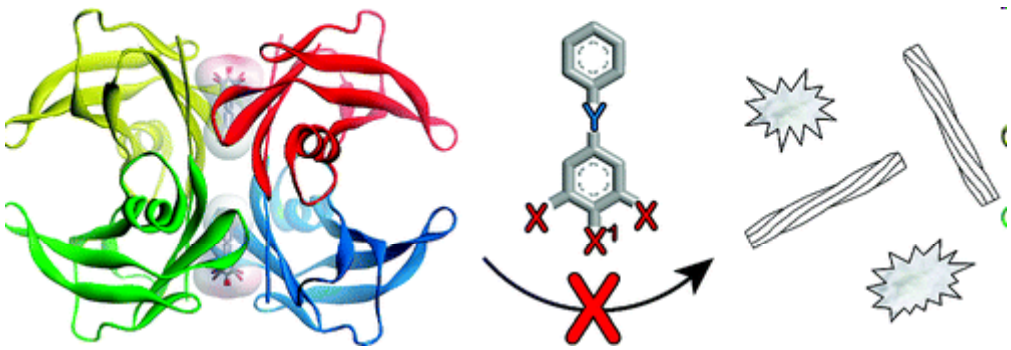
1. Prevent amyloid formation / stabilize monomer:
   - β-Secretase inhibitors
   - TTR-stabilizing drugs

Prevention of Transthyretin Amyloid Disease by Changing Protein Misfolding Energetics

Per Hammarström,* R. Luke Wiseman,* Evan T. Powers, Jeffery W. Kelly†

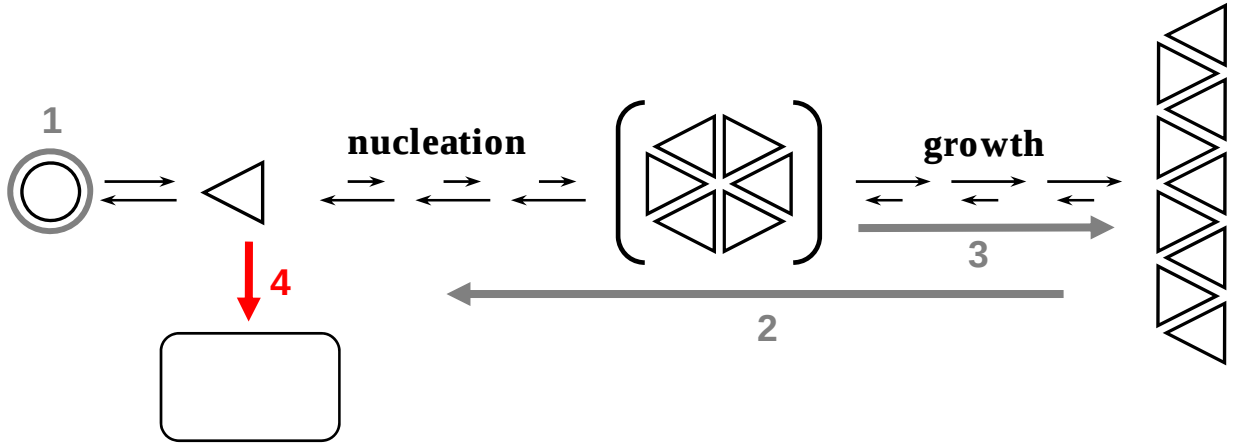


dissociation misfolding amyloid growth



Science 2003

Anti-amyloid intervention strategies



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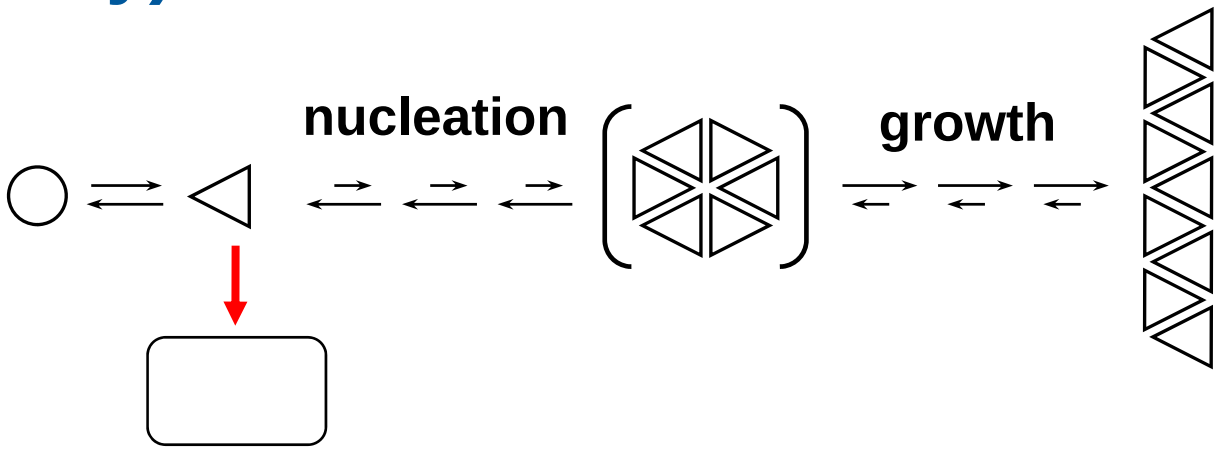
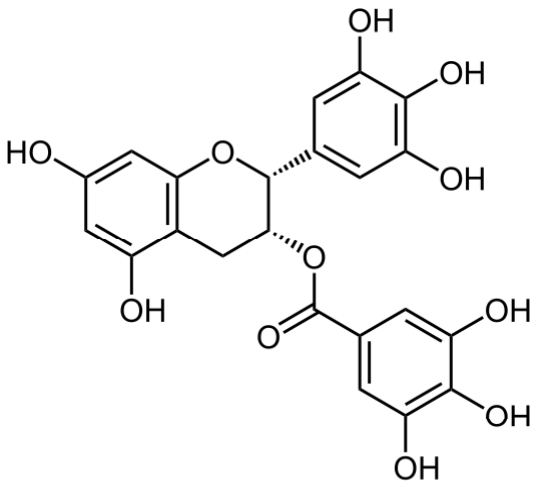
Redirecting amyloid aggregate formation (off-pathway)



Inducing the formation of non-amyloid aggregates reduces toxic oligomer and fibrillar species:

Epigallochatechin-3-gallate

(EGCG)



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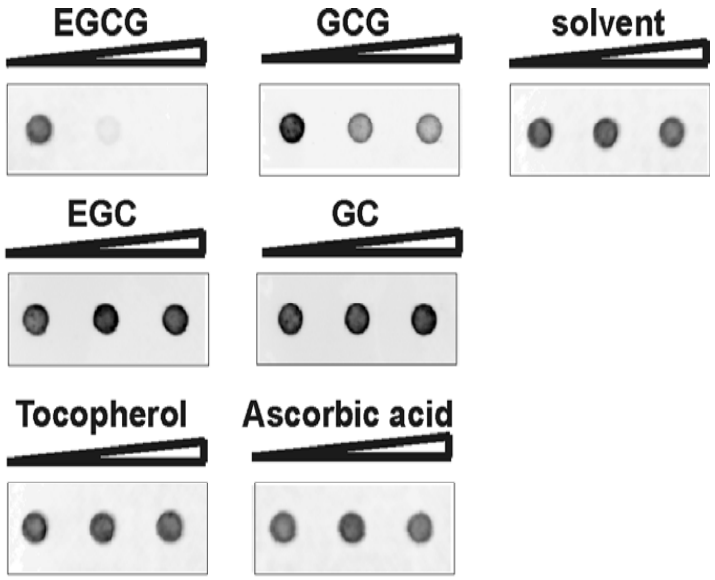
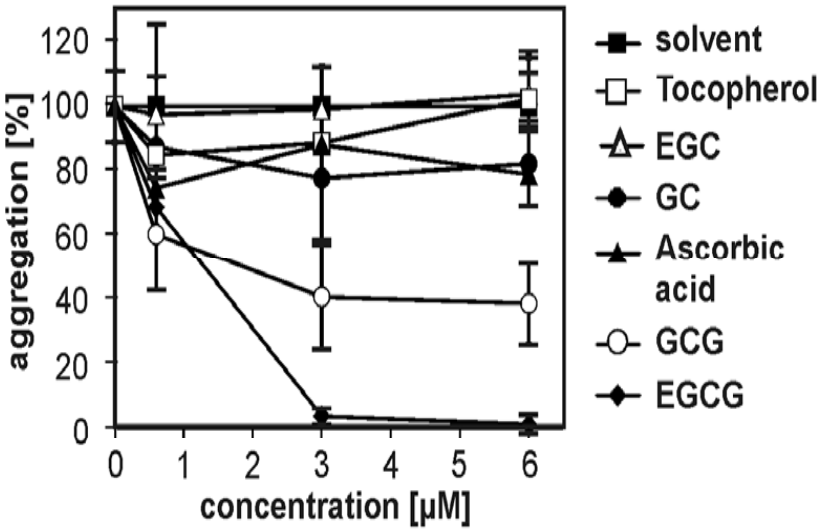
EGCG and GCG inhibit huntingtin aggregation





Ehrnhöfer et al. *Hum. Mol. Gen.* 2006

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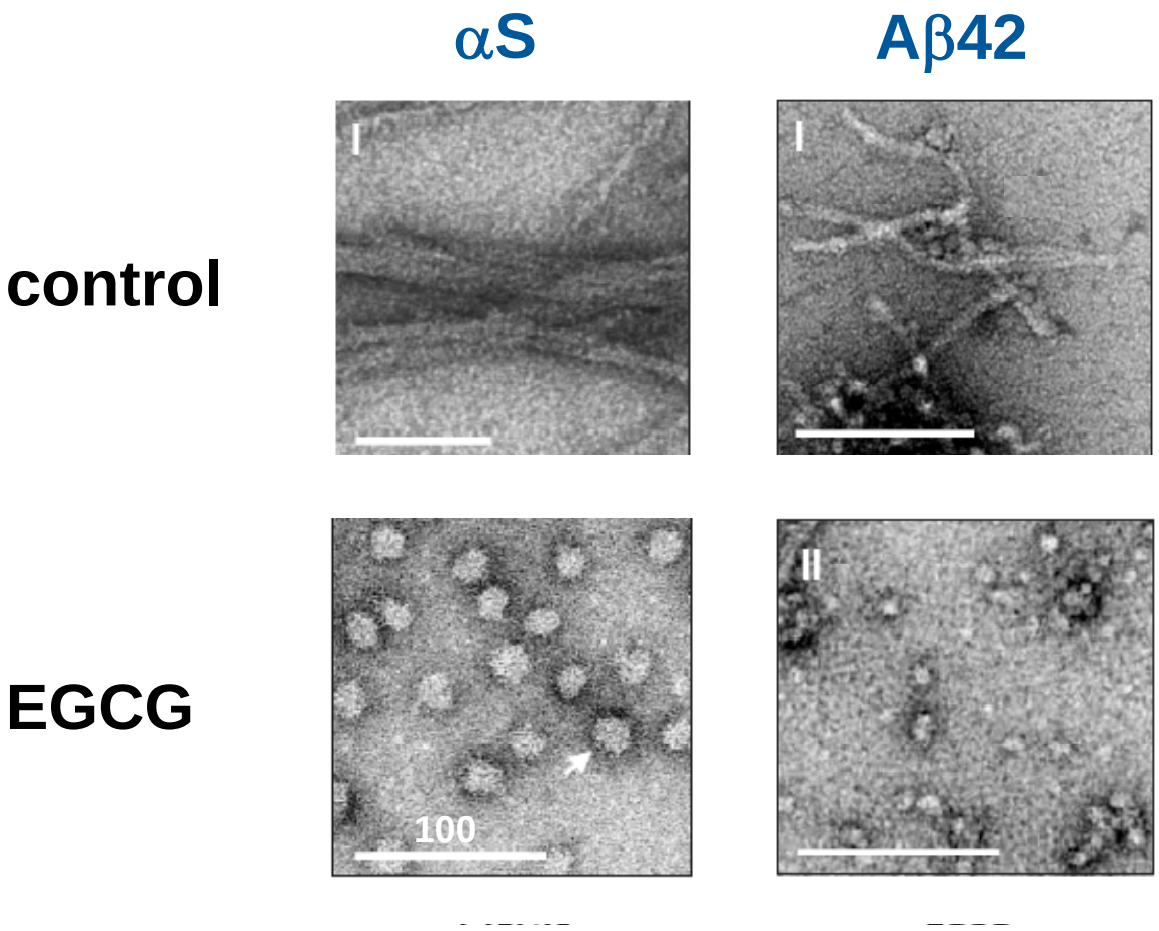
EGCG induces the formation of spherical / amorphous aggregates



Ehrnhöfer & Bieschke et al. Nature Struct. Mol. Biol. 2008

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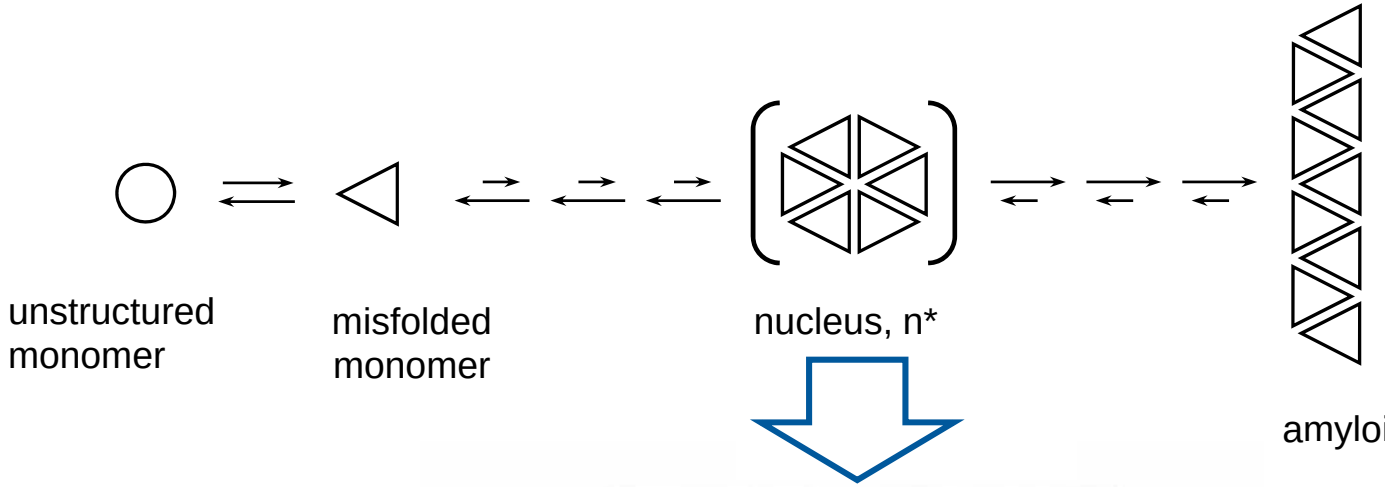
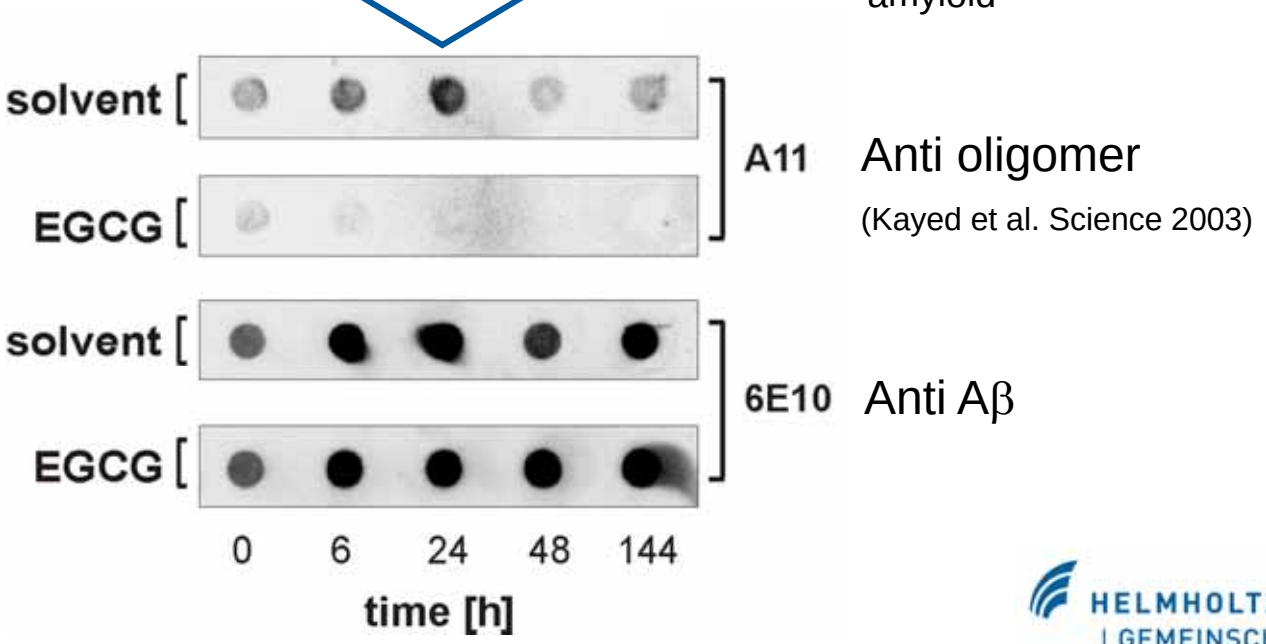
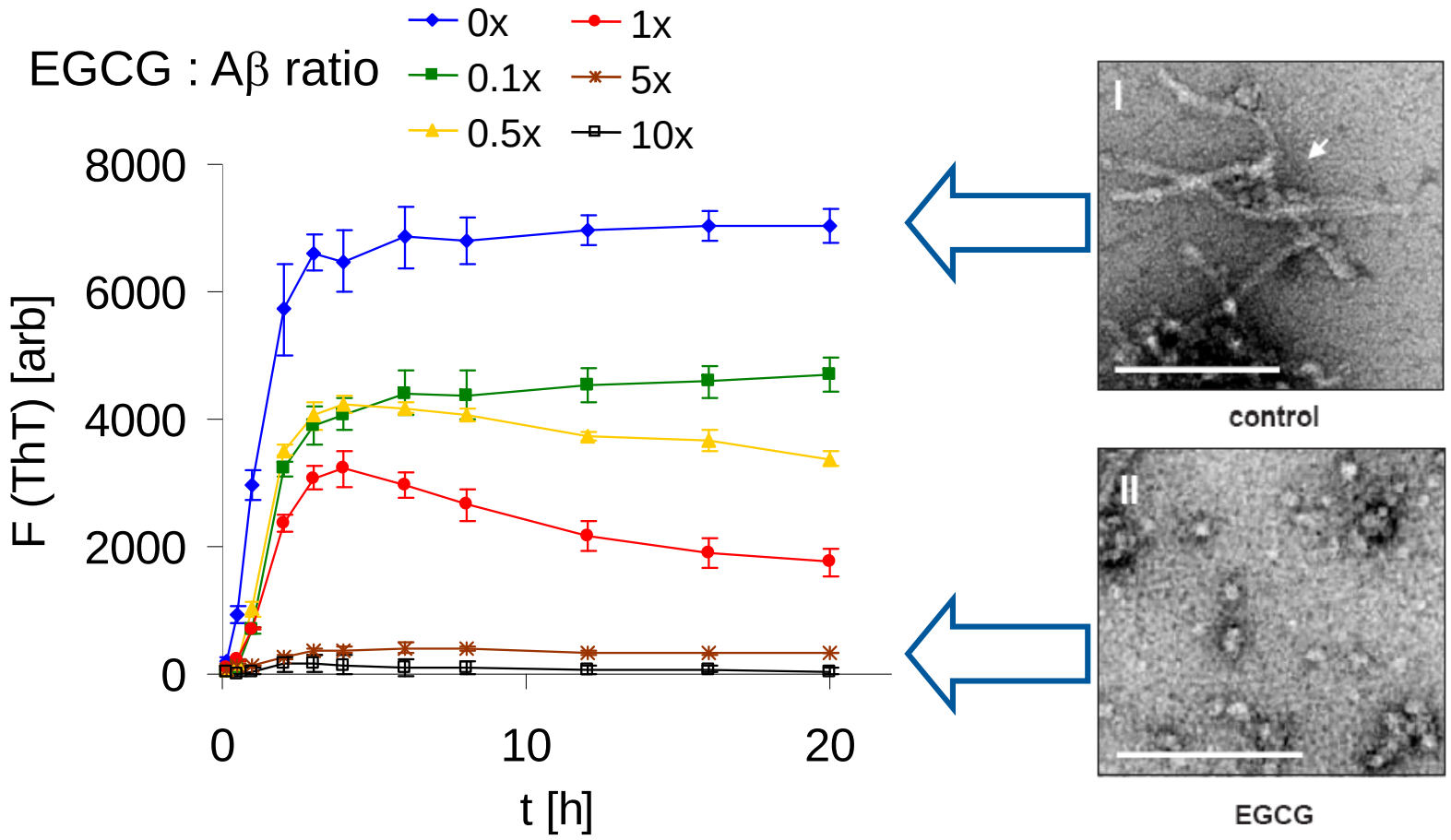
Anti-oligomer antibody A11 does not recognize EGCG-generated aggregates





EGCG-induced aggregates do not bind Thioflavin



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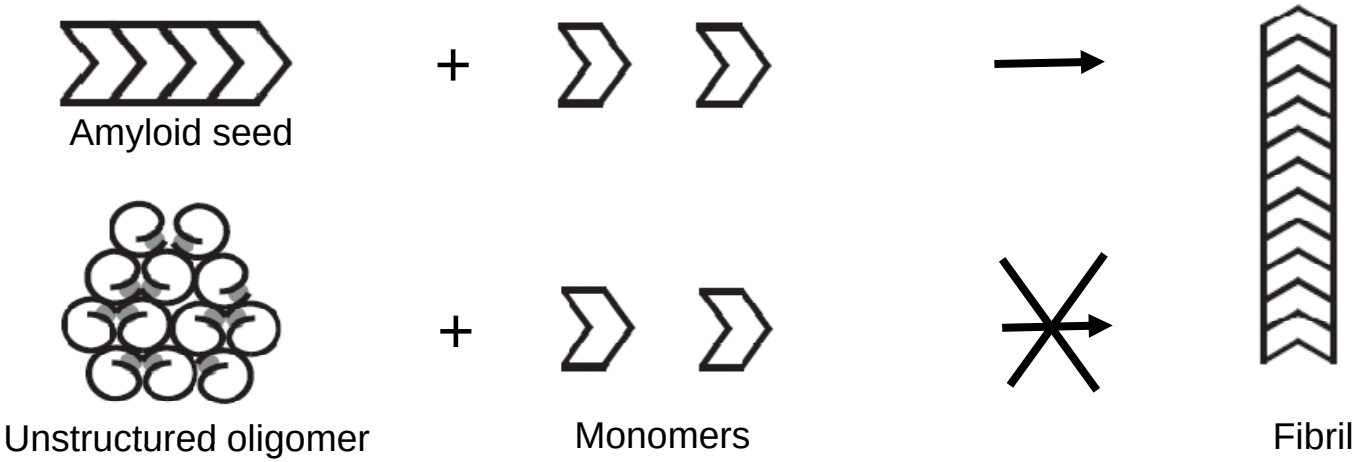
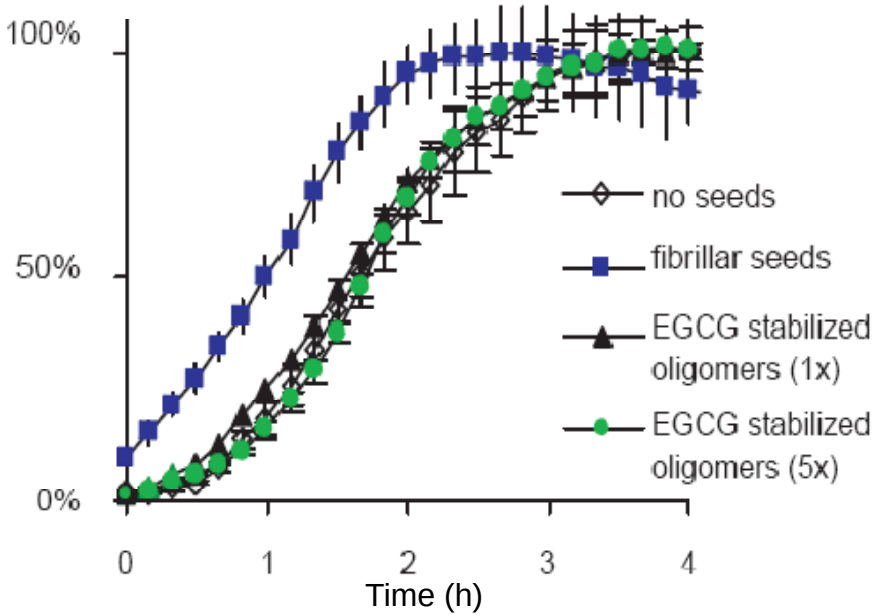
EGCG – induced and aggregates are not seeding-competent





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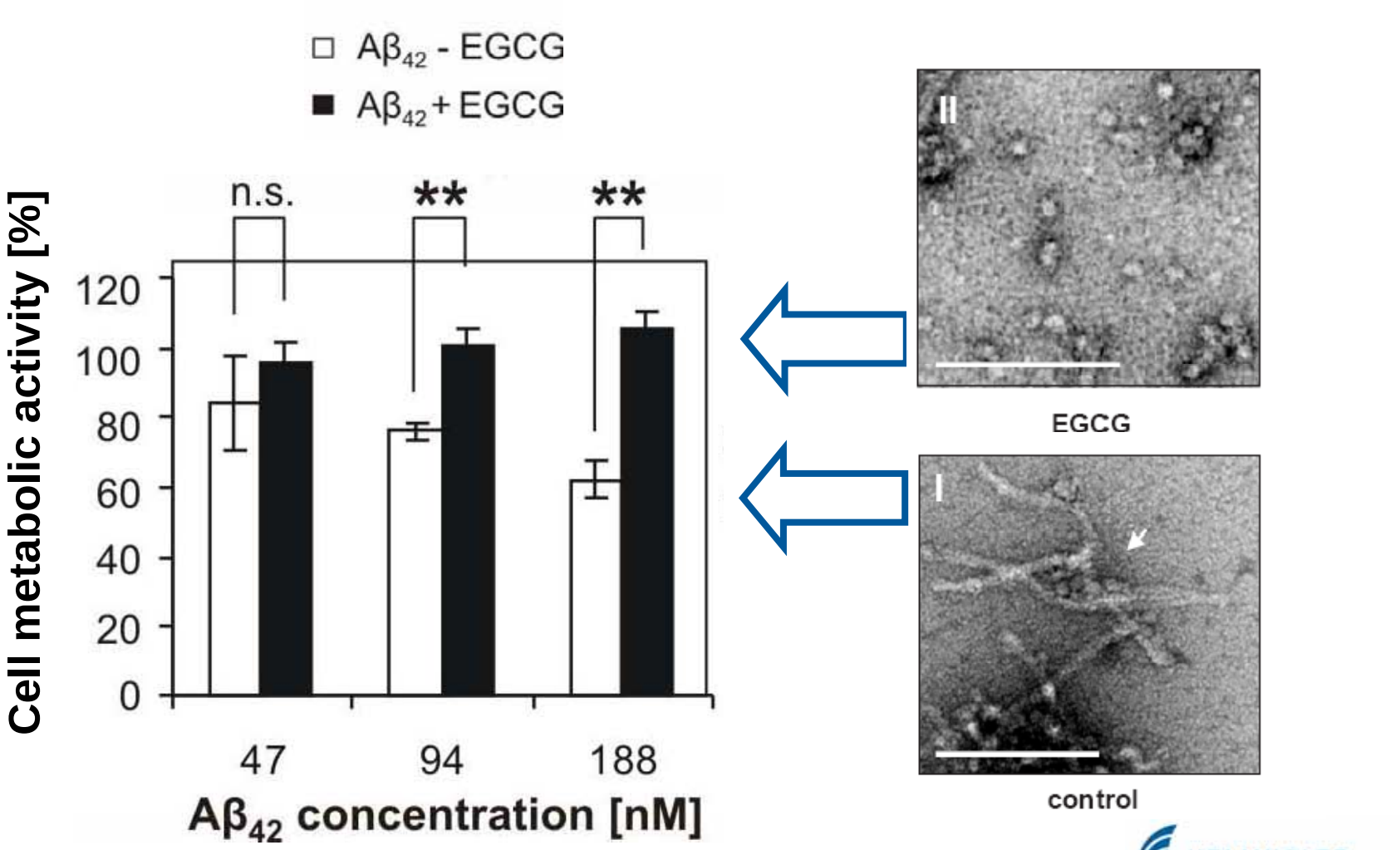
EGCG-induced Aβ42 aggregates are not toxic to PC12 cells



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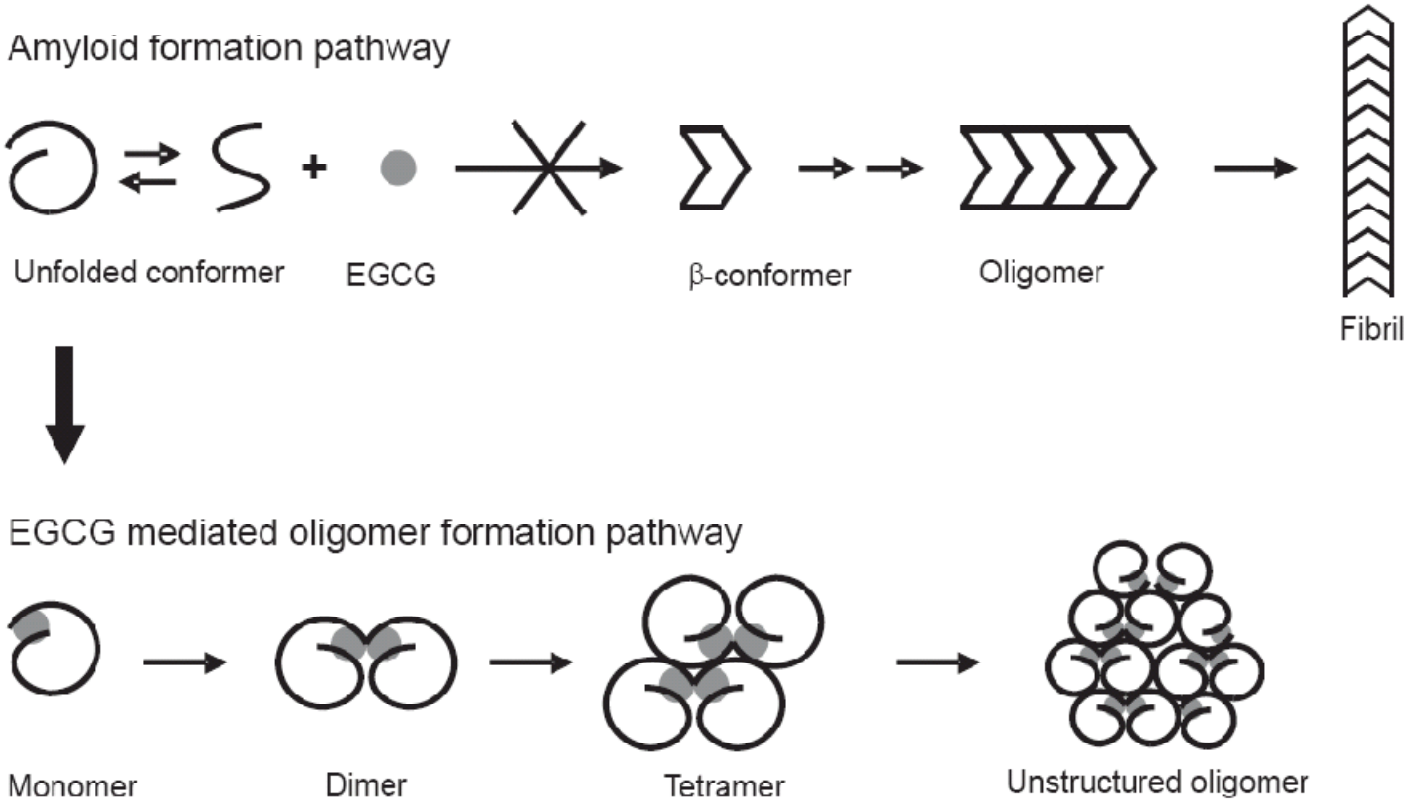
Model of EGCG induced off-pathway aggregation



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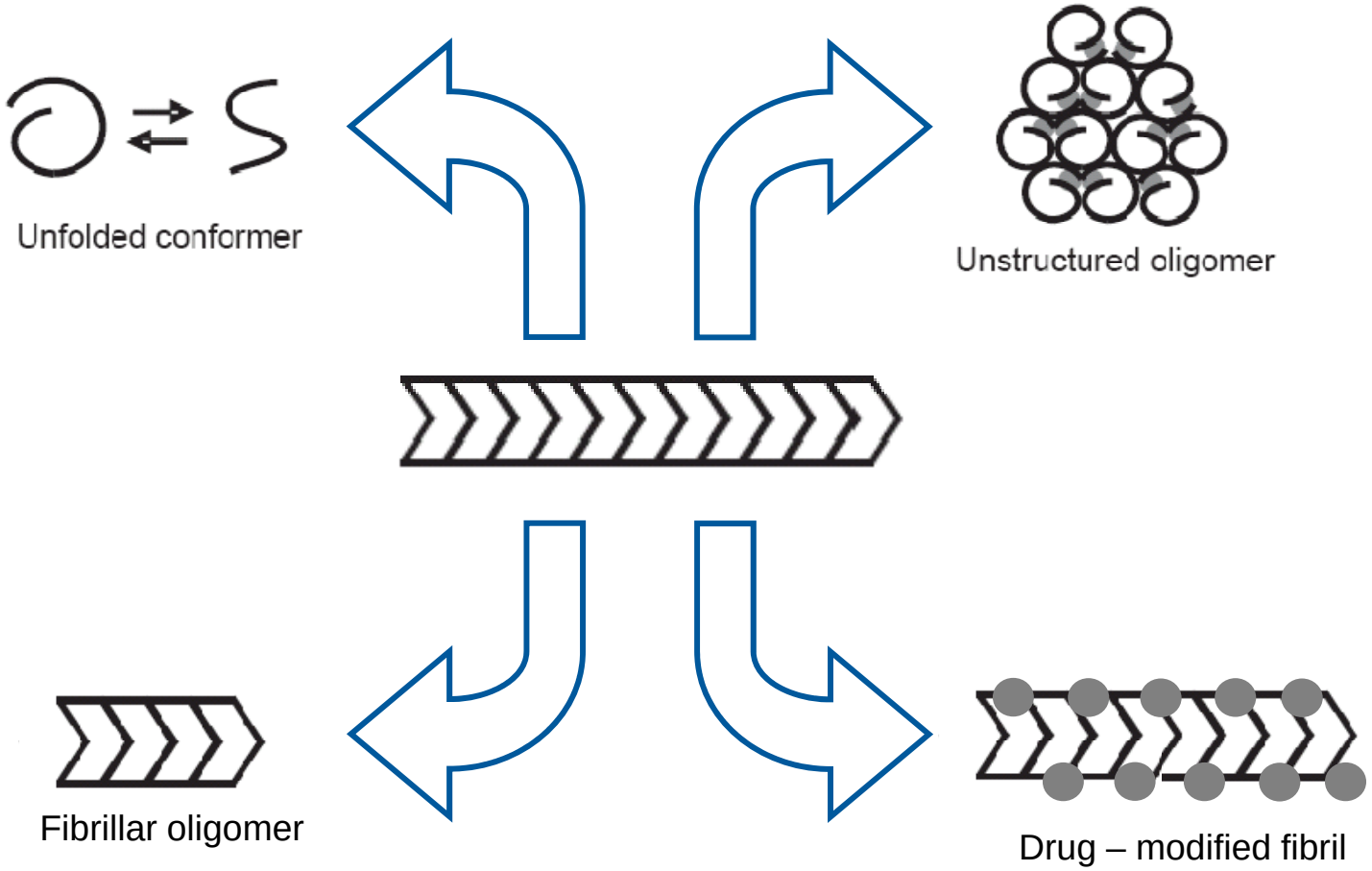
Future directions: Can small molecules disassemble amyloid fibrils?



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Future directions: Clinical efficacy of EGCG in amyloid diseases

- Possible therapeutic benefit of EGCG in light chain amyloidosis (Hunstein, Blood 2007)
- Planned clinical trials in LC-amyloidosis, systemic Transthyretin amyloidosis, Huntington's disease, Alzheimers disease

⇨ "German clinical green tea consortium"

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