Solving the Dilemma of Treatment Versus Prevention Strategies for Alzheimer's Disease

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Overview

- 3 major questions for the Alzheimer's field in terms of therapeutic discovery and development
  - Is the major hypotheses driving most of the therapeutic discovery wrong?
  - Are we conducting the right trials?
    - The treatment versus prevention paradox
  - What are the hindrances to identifying new targets in the downstream cascade that might make more effective therapies?
- Some ideas for a way forward

Question #1

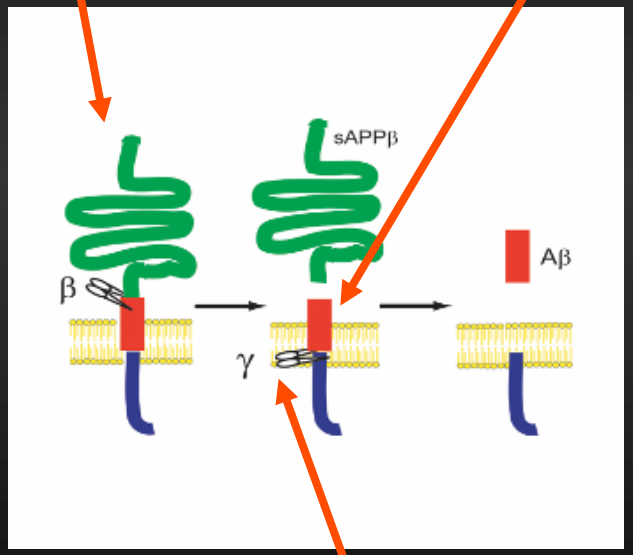
- Is the major hypotheses driving most of the AD therapeutic discovery wrong?

- Aβ Aggregate Hypothesis:
  - Aβ accumulation in misfolded protein triggers a complex cascade that result in neurodegeneration

AD Causing Genetic Alterations Alter Aβ Production in a Fashion that Promotes Aβ Aggregation

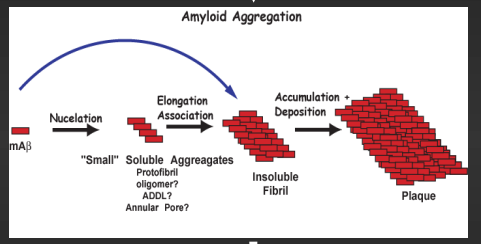
Trisomy 21/
APP gene
duplication

FAD-linked APP
mutations
chromosome 21

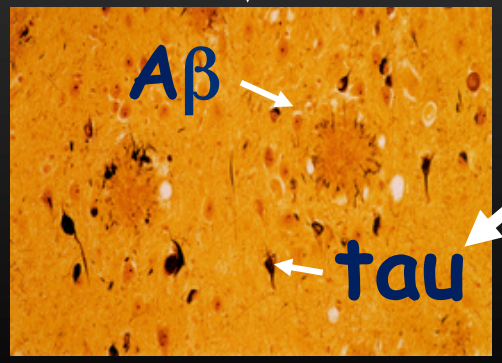


FAD-linked
Presenilin mutations
(chromosome 14 and 1)

↑Aβ42
↑Aβ40 and Aβ42
More amyloidogenic Aβ



APOE
Clusterin
SorL1
CR1

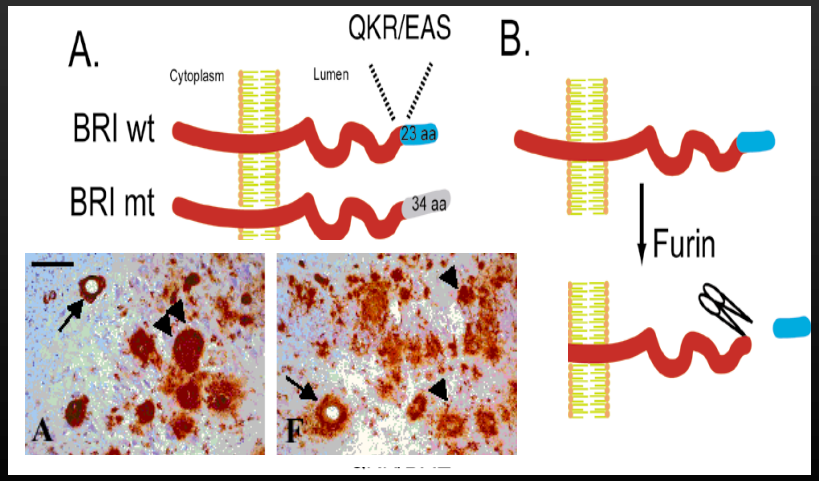


MAPT
Mutations

Neurodegeneration

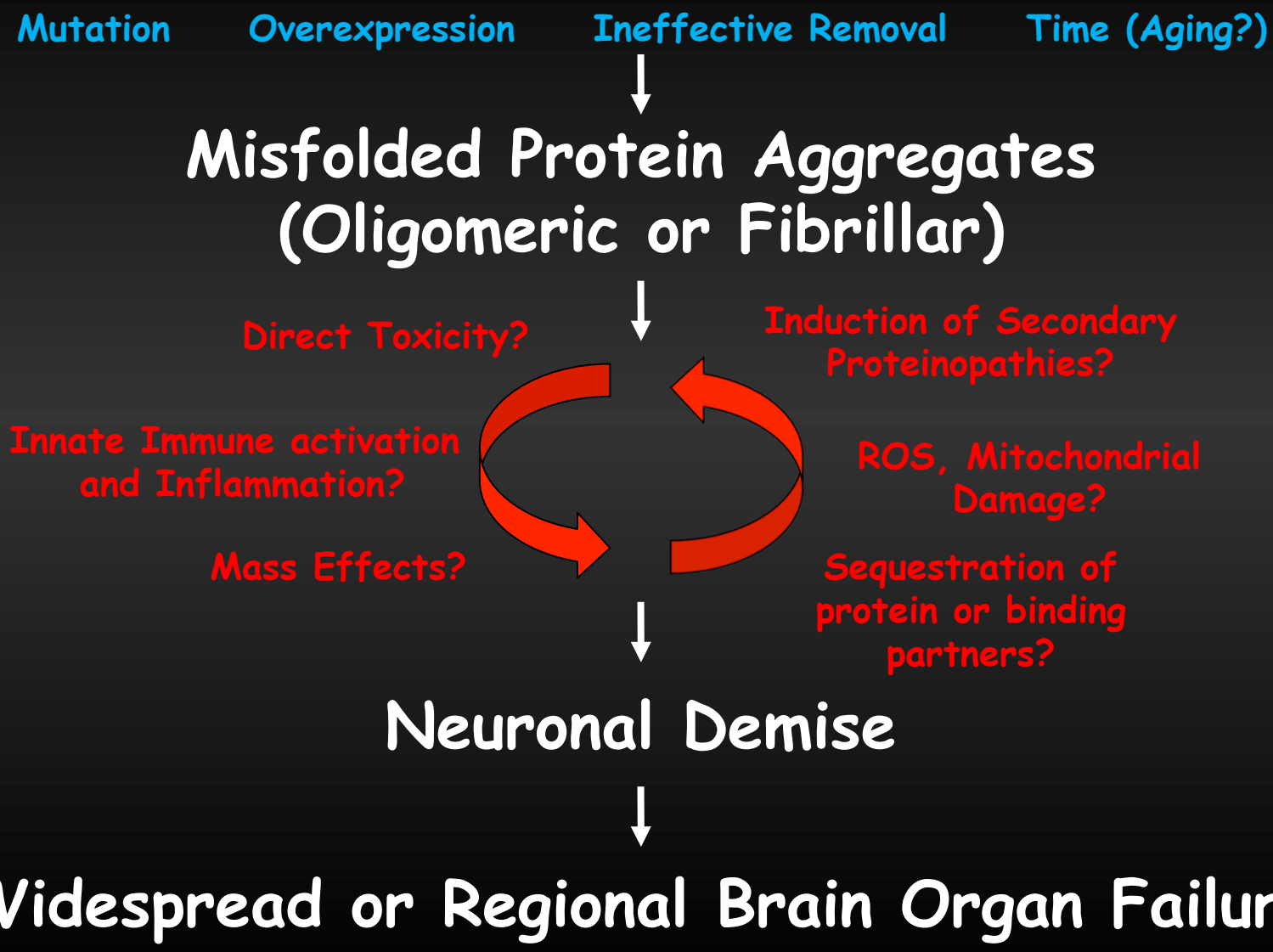
British and Danish Familial Dementia: Other CNS Amyloidoses

- dementia, spastic paraparesis and ataxia
- cerebrovascular amyloid, and amyloid in non-neuritic plaques, tangles, neuronal loss, further support for a cascade
- Mutations in BRI2 (ITM2B) result in production of amyloidodogenic peptides (Abri and Adan) (Vidal et al Nature 1999, PNAS 2000)
- Provide additional strong support that accumulation of amyloidogenic peptides causes neurodegeneration



Rostango et al JBC 2002

Proteinopathies and Neurodegeneration



A key assumption that underlies the Aβ aggregate hypothesis

- The fundament pathological cascades in sporadic AD are the same as in genetic forms
  - Likely to be true for the majority of what we define as sporadic AD
  - However, especially in the 80+ year old population the AD dementia phenotype may represent a convergence of independent pathologies and not necessarily a single cascade (e.g., Small and Duff Neuron 2008)
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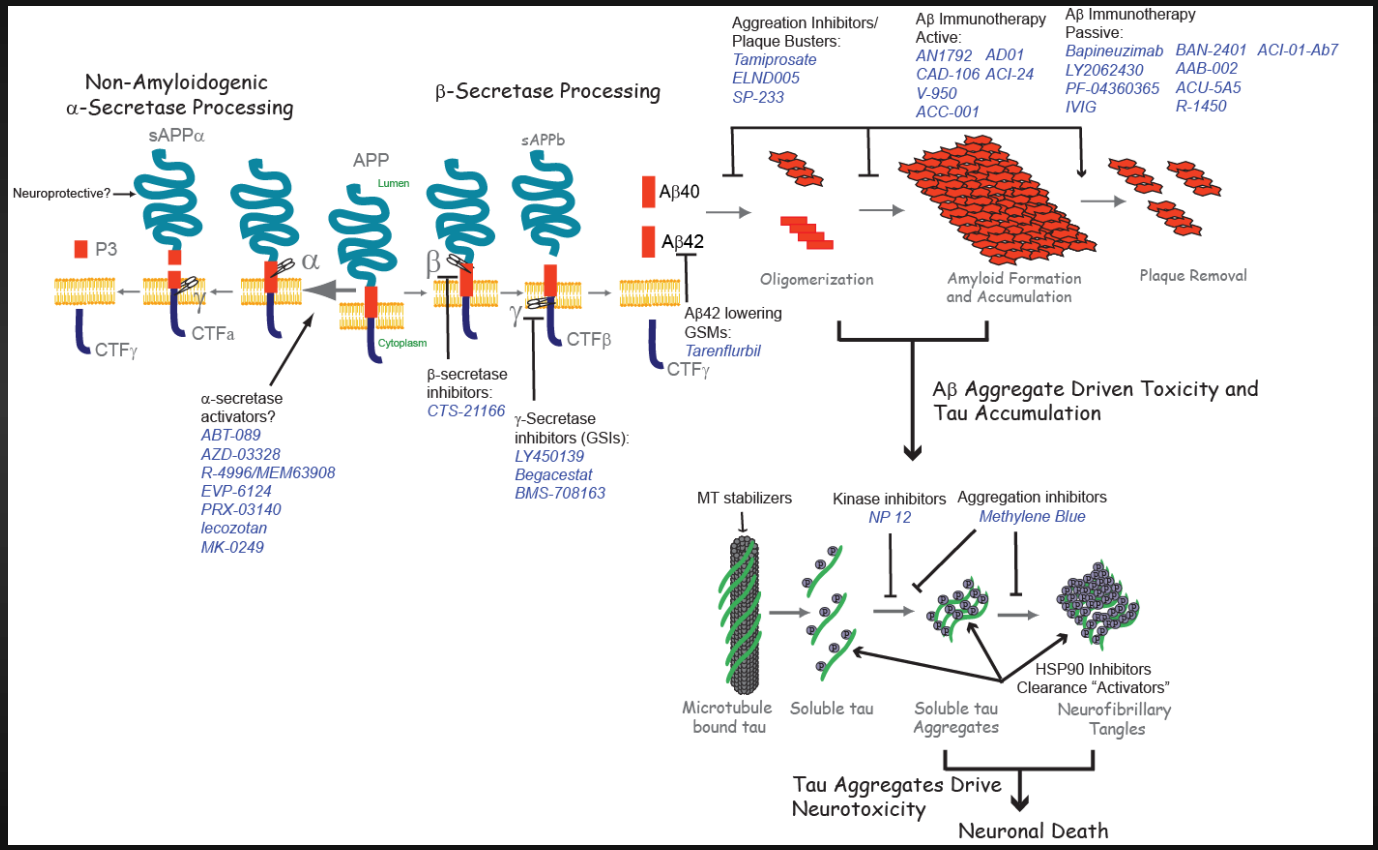
Question #1

- Is the major hypotheses driving most of the AD therapeutic discovery wrong

- Aβ Aggregate Hypothesis:
  - Aβ accumulation in misfolded protein triggers a complex cascade that result in neurodegeneration

The Aβ Aggregate Hypothesis Has Provided a Framework for Therapeutic Discovery



~30 Therapies targeting Aβ and few targeting tau are being tested in humans

Question #2

- Are we conducting the right trials?
  - Window Therapy Studies with GSIs
    - Pritam Das, Christophe Verbeeck, Ann Marie Baine, Kim Malphus
    - Abdul Fauq, Ghulam Mahravi

      Supported by the NIA
  - Passive Immunotherapy in APP inducible mice
    - 7/14/2010 2:00:00 PM
      O4-08-05. Robust Amyloid Clearance In A Mouse Model Of AD Provides Novel Insights Into The Mechanism Of Abeta Immunotherapy
      Allan Wang, B.S.1,2, Pritam Das, Ph.D.3, Robert C. Switzer, III, Ph.D.4, Todd E. Golde, M.D., Ph.D. 5, Joanna L. Jankowsky, Ph.D.1.
  - The Treatment versus Prevention Paradox

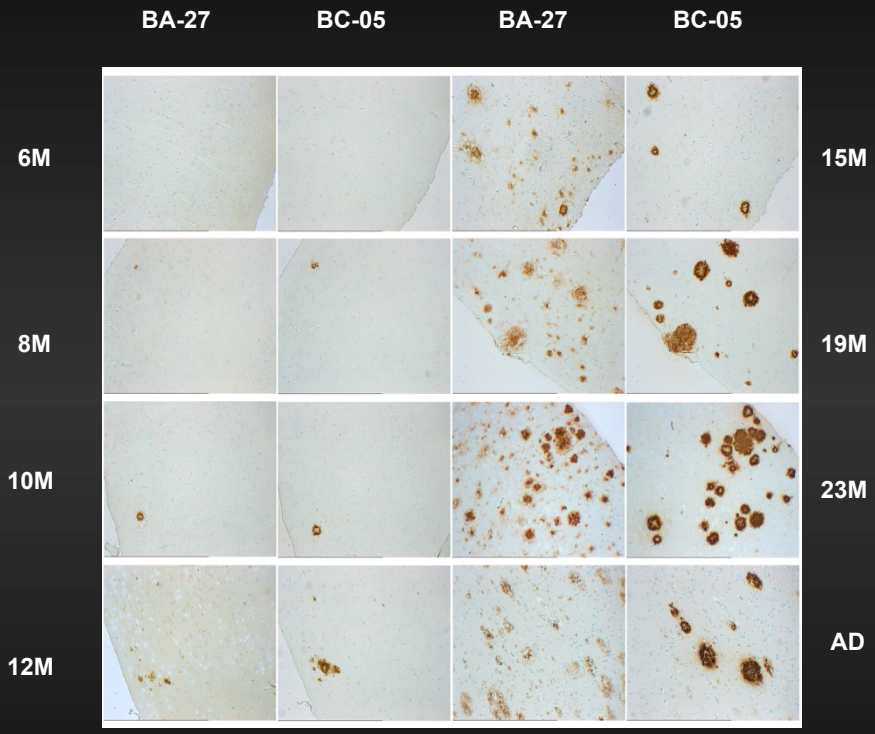
Targeting Aβ: what's the magnitude of the problem

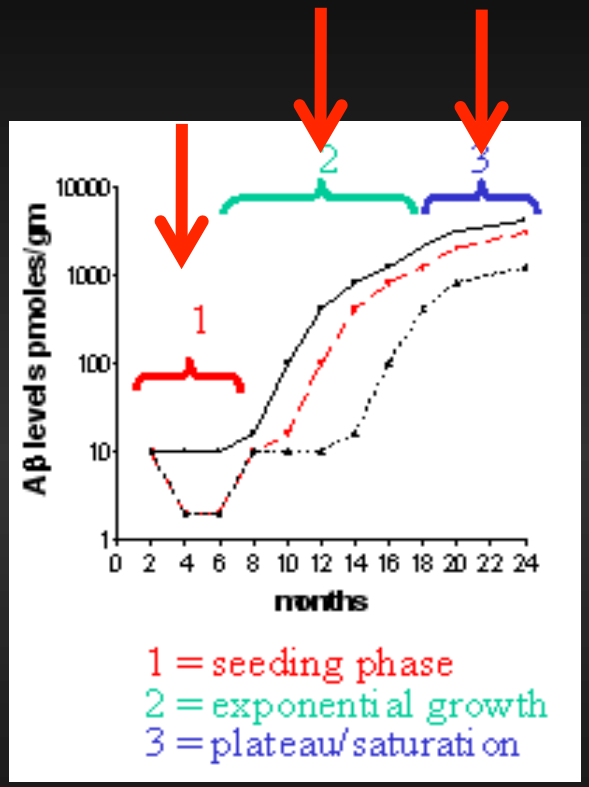
- In humans with AD ~10+ μmoles of Aβ accumulate (~100 mg).
  - = Aβ produced in the brain in ~2-5 years.
  - During the deposition phase what percentage of Aβ is depositing?
  - If its 50%? Means 4-10 year deposition phase…

- In a 21 month old "AD-like" (at least with respect to plaque pathology) APP mouse model about 10 nmoles (45 μg) of Aβ accumulate.
  - = Aβ produced in brain in 20-40 days

Levites et al FASEB 2006

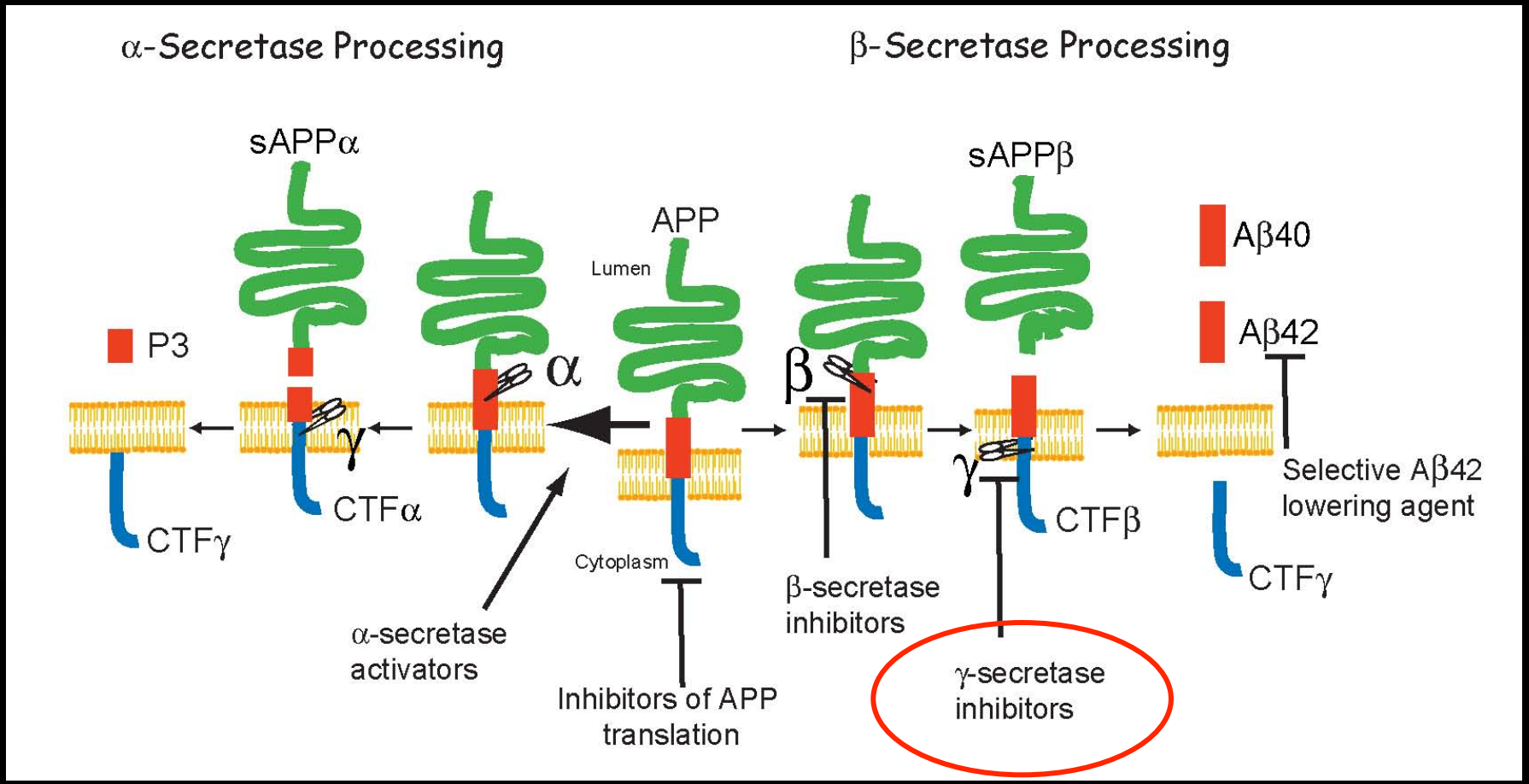
When and to what extent do you have to decrease Aβ production?





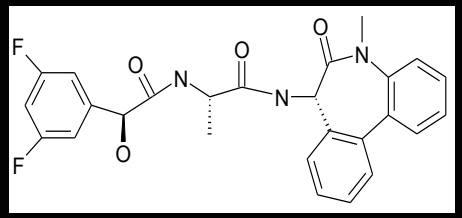
Aβ amyloid formation is a nucleation dependent polymerization reaction and deposition in models appears to mimic this process

GSI studies targeting Aβ Production



GSI studies using LY-411,575

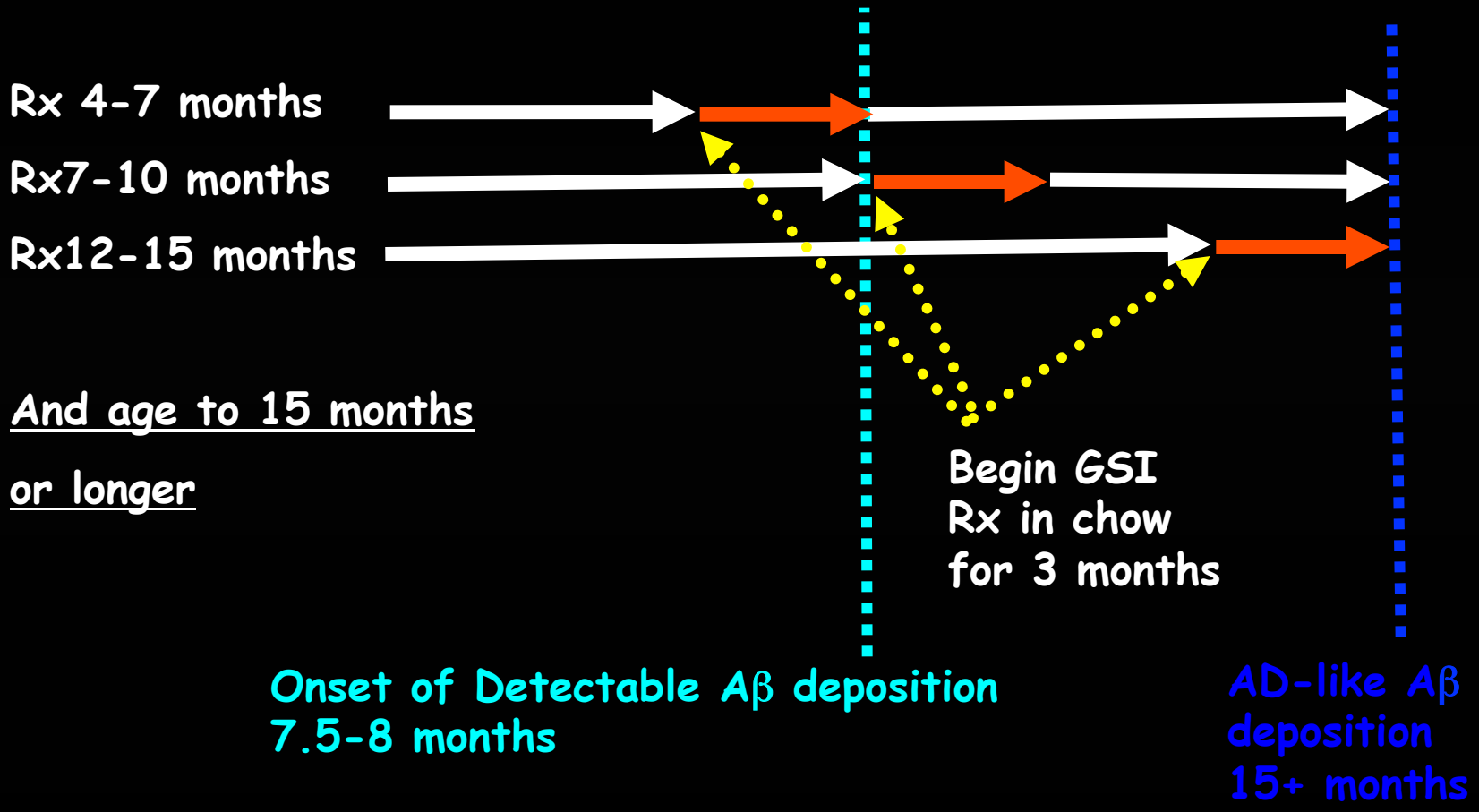
- Potent GSI active against APP and Notch cleavage (no apparent selectivity in vitro)
- Should inhibit cleavage of any γ-secretase substrate
- Orally bioavailable, brain penetrant
- Narrow Therapeutic range
- Not an active site inhibitor



Compound	Mice	Route	Dose mg/kg/day	Length of Treatment	% Aβ40 Reduction *Brain*	% Aβ40 Reduction *Plasma*	Overt Toxicity
LY411575	Tg2576	Oral (Chow)	2.5	>2 weeks	55%	74%	NO
			5	<2 weeks	77%	93%	YES*

*morbidity and mortality (skin lesions, bloating, intestinal bleeding, diarrhea)

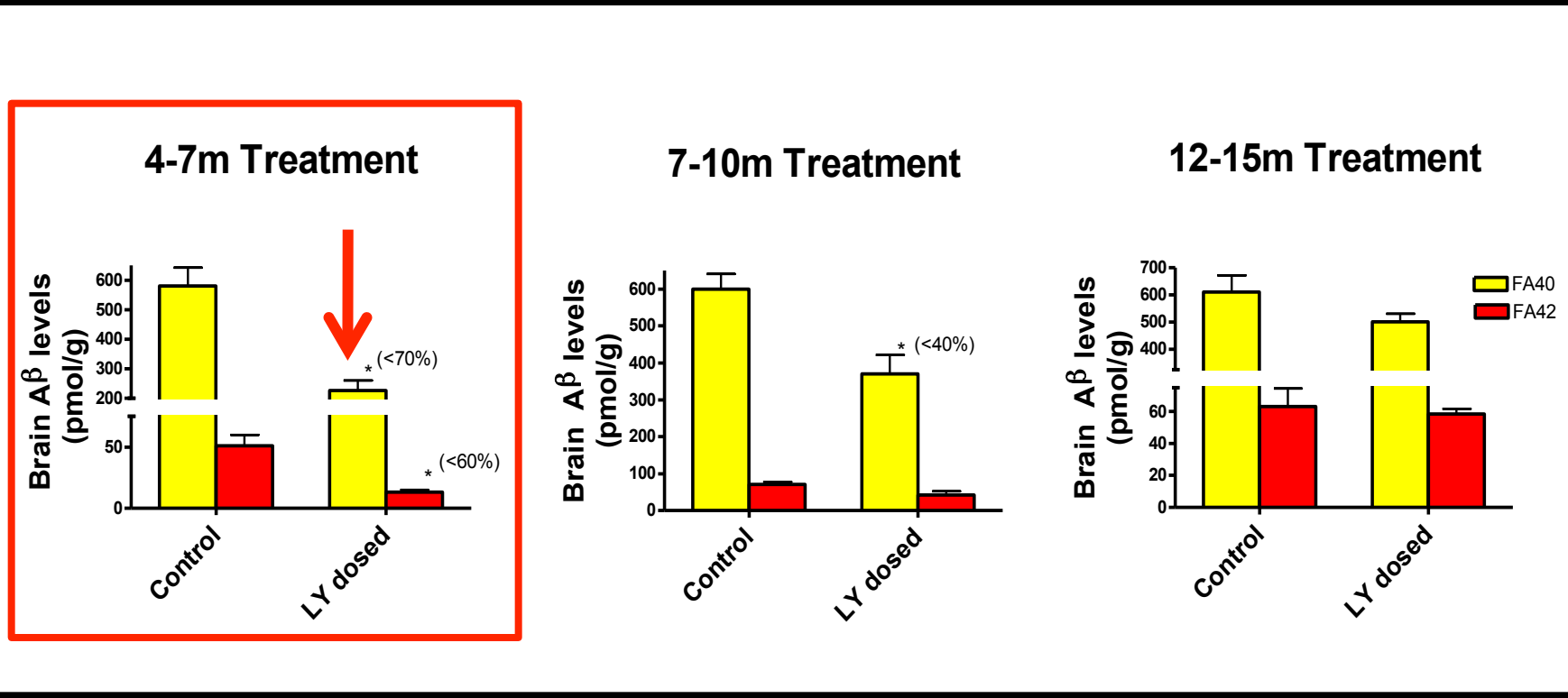
"Window" therapy with a GSI (LY) (50% reduction in Aβ production)



When, and to what extent, do you have to decrease Aβ production?

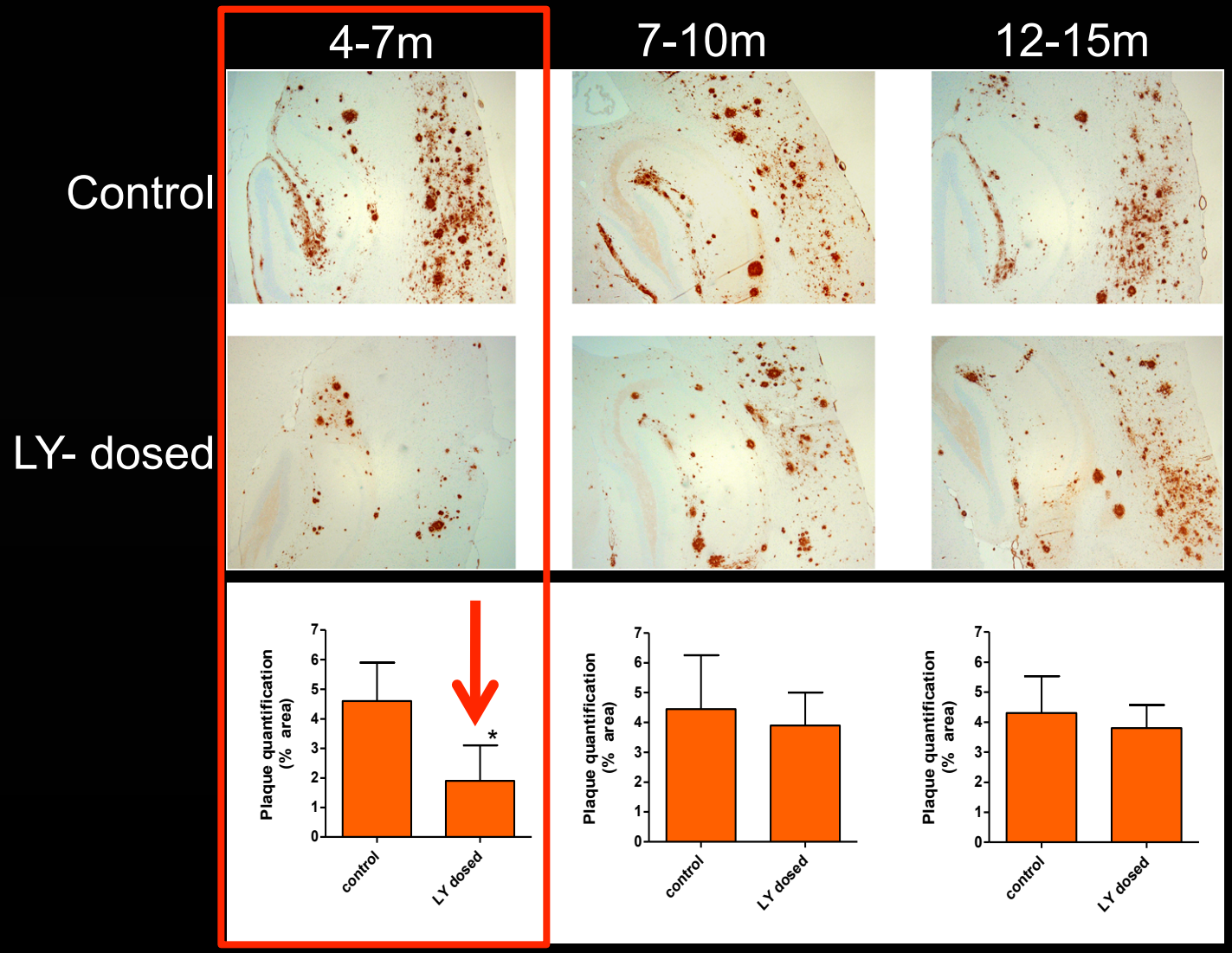
- Can one predict the outcome?
  - If Aβ has not begun to deposit, will lowering its production by ~50% have any effect?
    - Age (time) versus aging effect
  - In mouse models Aβ deposition is exponentially increased with age until it reaches a plateau in late life.
    - Reductions in production during the exponential phase should translate into large reductions in deposition?
    - Indeed, amyloid formation is a concentration dependent phenomena

4-7 Month Window Rx Is More Efficacious at Reducing Aβ Deposition at 15 Months of Age



Data representative of 2+ independent experiments
8-10 Tg2576 mice per group
Effect persists at 18 months for 4-7M Rx group

Earlier Rx Is More Efficacious at reducing Aβ Deposition



Conclusions: Initial Studies of GSI Window Therapy

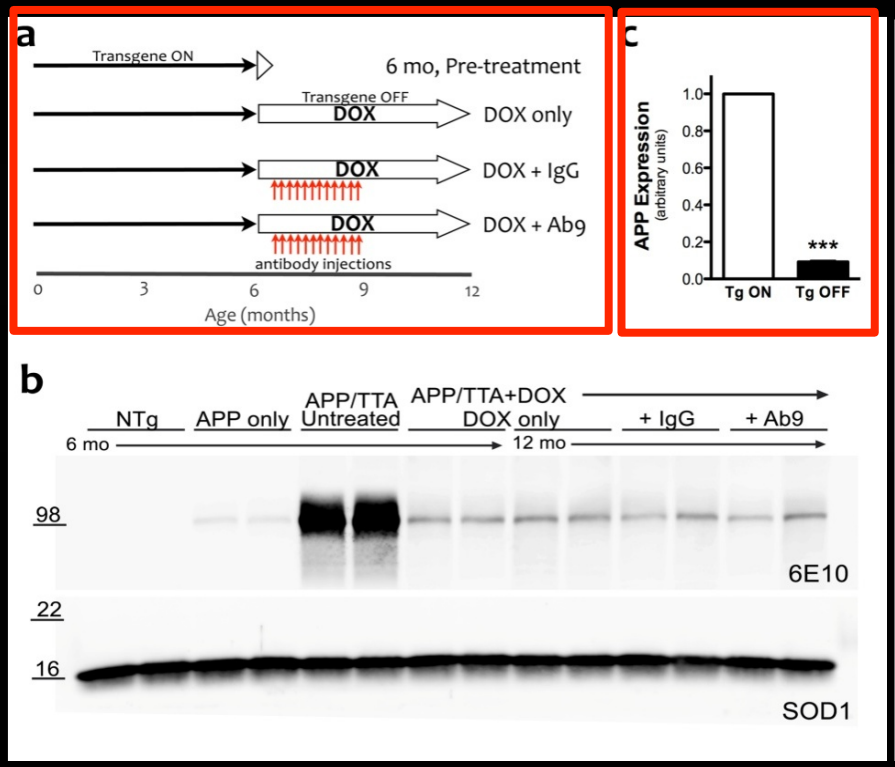
- Early reductions in Aβ provide a prolonged robust effect even after D/C of Rx
  - Exponentially more Aβ per unit time is deposited in the later Rx windows
  - Reversal of nucleation events (seeds) during this pre-deposition phase of treatment?
  - Once seeded amyloid formation proceeds despite lowering Aβ production by >50%
  - Age not aging is critical
- Support Prophylactic rather then therapeutic targeting of Aβ for AD
- NSAIDs, Statins, Estrogen etc all fail in therapeutic trials but epidemiology supports a protective effect

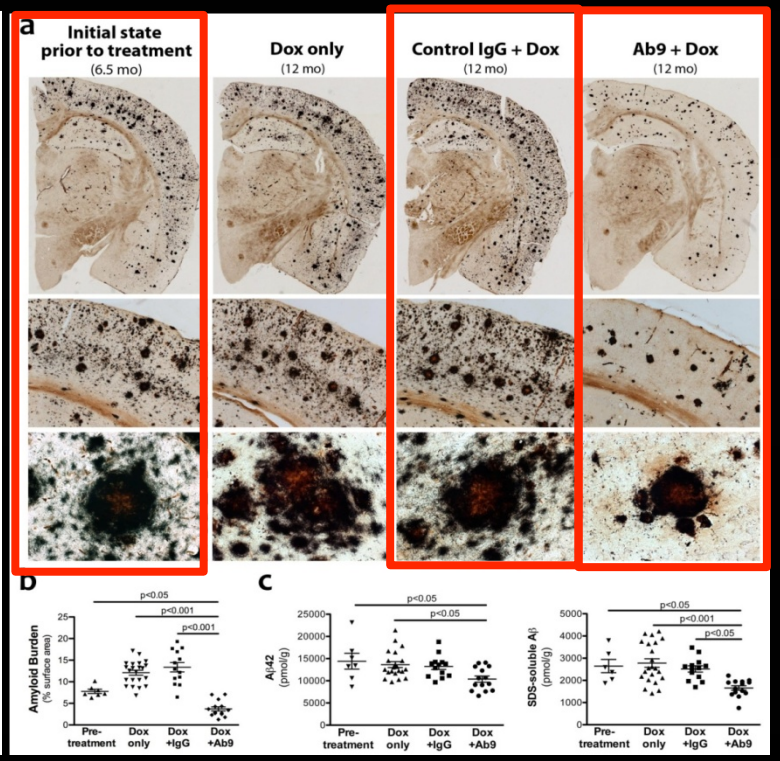
Caveats and thoughts

- Caveats:
  - CNS production of Aβ per unit time in mouse models is higher then in most humans
  - Behavioral studies were confounded by use of this GSI
  - GSIs are the only modality we have looked at to date
    - However in almost all therapeutic modalities examined in APP mice the law of diminishing returns applies (e.g, Das et al NBA 2001, Karolinski et al J Nsci 2009)
      - Notable exceptions. E. g., town et al 2009 Nat Med "Blocking TGF-beta-Smad2/3 innate immune signaling mitigates Alzheimer-like pathology"
- Thoughts
  - Seeding or Nucleation is a critical potentially reversible phenomenon in CNS proteinopathies that we poorly understand
  - What about multimodal therapy?

Clearance of Plaques in Inducible APP mice (Collaboration with Joanna Jankowsky, Baylor)

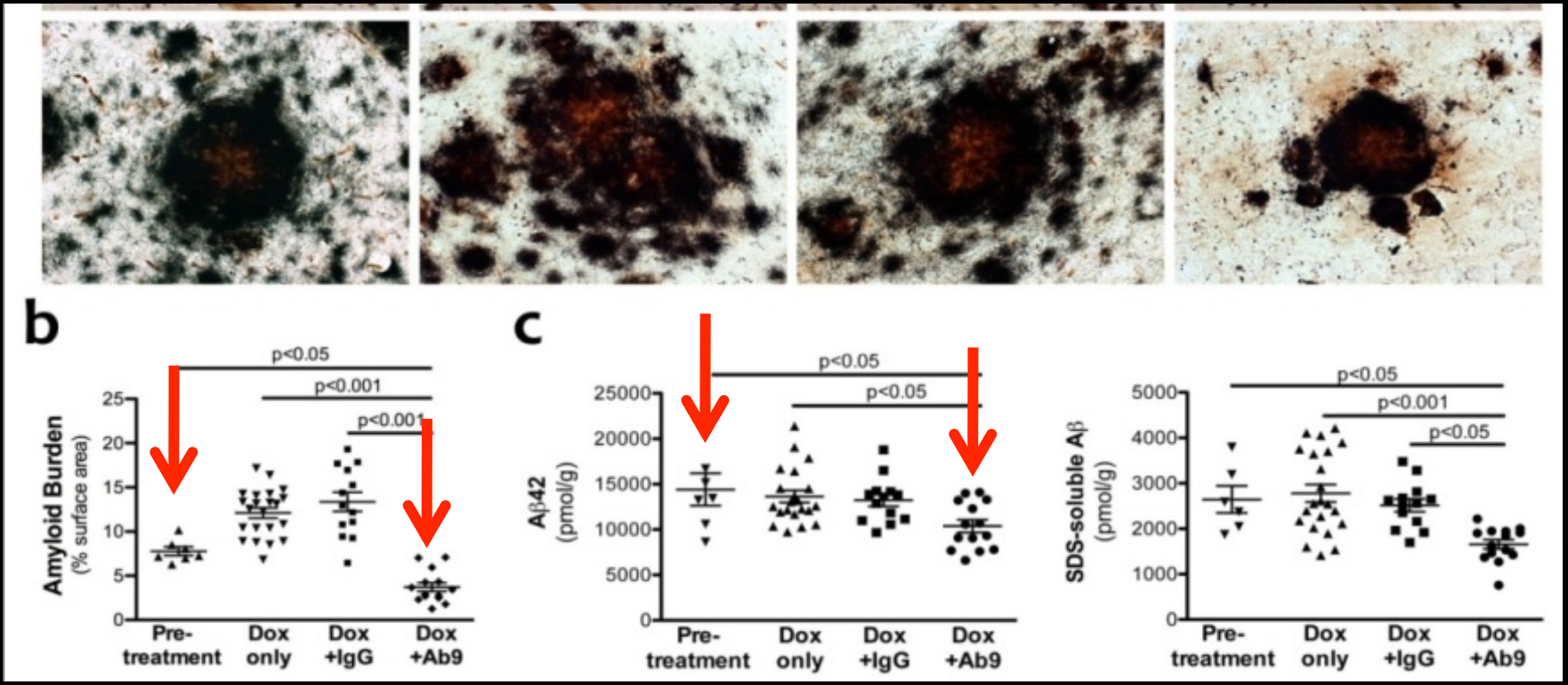
Mimics maximal likely effect with a secretase inhibitor and passive immunotherapy





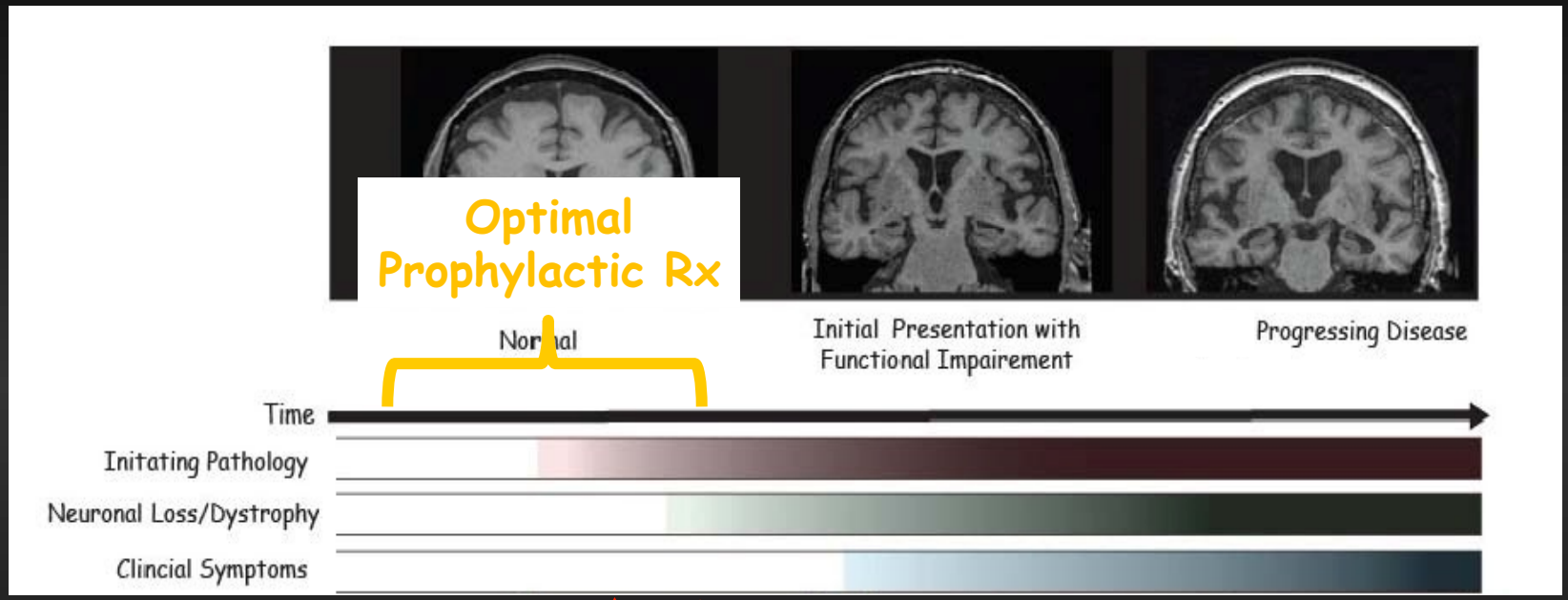
To alter pre-existing deposits requires intensive therapy

Clearance of Plaques in Inducible APP mice (Collaboration with Joanna Jankowsky, Baylor)



Under "optimal" conditions some preexisting Aβ deposits can be cleared

Are we doing the wrong trials in AD?



age 60 75 90

Aβ deposition begins

Aβ deposition plateaus
CSF Aβ drops

Tau CSF rises

Intervention in
Symptomatic Patient
with Trigger Targeting Rx?

The Treatment vs. Prevention Paradox

- There is extensive damage to the brain by the time even MCI of the AD type (prodromal AD) is detected
- Disease modifying therapies targeting the upstream "triggers" (e.g. Aβ, tau) are likely to be most effective as preventive Rxs, and may have little or no effect in symptomatic patients
- Current trial design involves treatment not prevention

1,026 Experimental Treatments in Acute Stroke

Victoria E. O'Collins, B.Sci,[1] Malcolm R. Macleod, MRCP, PhD,[3] Geoffrey A. Donnan, MD, FRACP,[2] Laura L. Horky, MD, PhD,[2] Bart H. van der Worp, MD, PhD,[4] and David W. Howells, PhD[1]

- 114 made it to the clinic
- 1 Approved (TPA)
- No evidence that TPA was superior in preclinical studies
- Concerns that preclinical studies and clinical trial design were poorly matched

- We are not going to have 114 "at bats" and no hits in AD disease modifying therapy trials

We can't afford to many more strikeouts in phase III

NSAIDs and enantiomers of flurbiprofen target γ-secretase and lower Aβ42 in vivo

See the related Commentary beginning on page 321.

Jason L. Eriksen,[1] Sarah A. Sagi,[2] Tawnya E. Smith,[1] Sascha Weggen,[2] Pritam Das,[1] D.C. McLendon,[1] Victor V. Ozols,[1] Kevin W. Jessing,[3] Kenton H. Zavitz,[3] Edward H. Koo,[2] and Todd E. Golde[1]

JAMA®

Online article and related content current as of February 16, 2010.

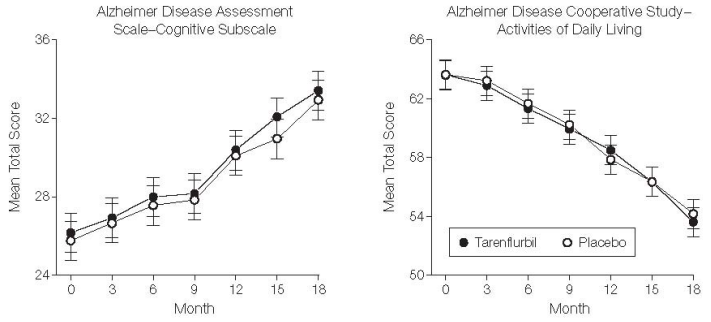
Effect of Tarenflurbil on Cognitive Decline and Activities of Daily Living in Patients With Mild Alzheimer Disease: A Randomized Controlled Trial

Robert C. Green; Lon S. Schneider; David A. Amato; et al.

JAMA. 2009;302(23):2557-2564 (doi:10.1001/jama.2009.1866)

http://jama.ama-assn.org/cgi/content/full/302/23/2557

Figure 2. Alzheimer Disease Assessment Cognitive Subscale and Alzheimer Disease Cooperative Studies–Activities of Daily Living Scale Scores by Visit



No.

Tarenflurbil	837	772	778	779	779	780	789
Placebo	806	741	746	746	746	746	749

803	756	770	774	774	774	783
777	725	747	749	750	750	752

Values represent means using imputed last observation carried forward. Error bars represent 95% CIs.

Compounds tested in phase 3 for disease modification were not optimal anti-Aβ therapies

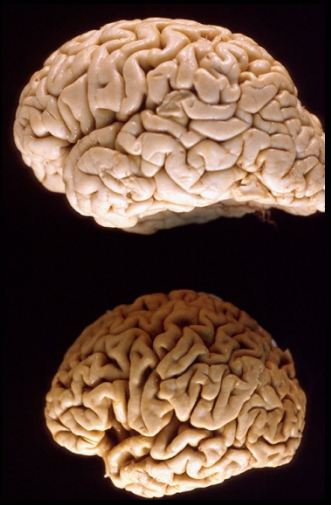
Flurizan a weak γ-secretase modulator with numerous other actions (e.g., NFkB inhibition) with suboptimal PK, superb trial, no evidence for efficacy

Alzhemed a weak aggregation inhibitor, suboptimal execution of clinical trial?

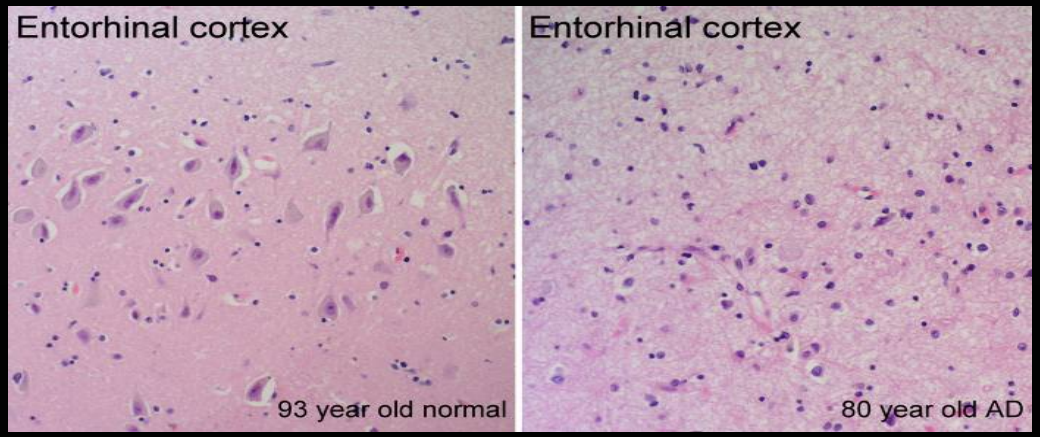
Question #3

What are the hindrances to identifying new targets in the downstream cascade that might make more effective therapies

The extent to which mutant APP or Aβ based models mimic the complete AD phenotype is debatable



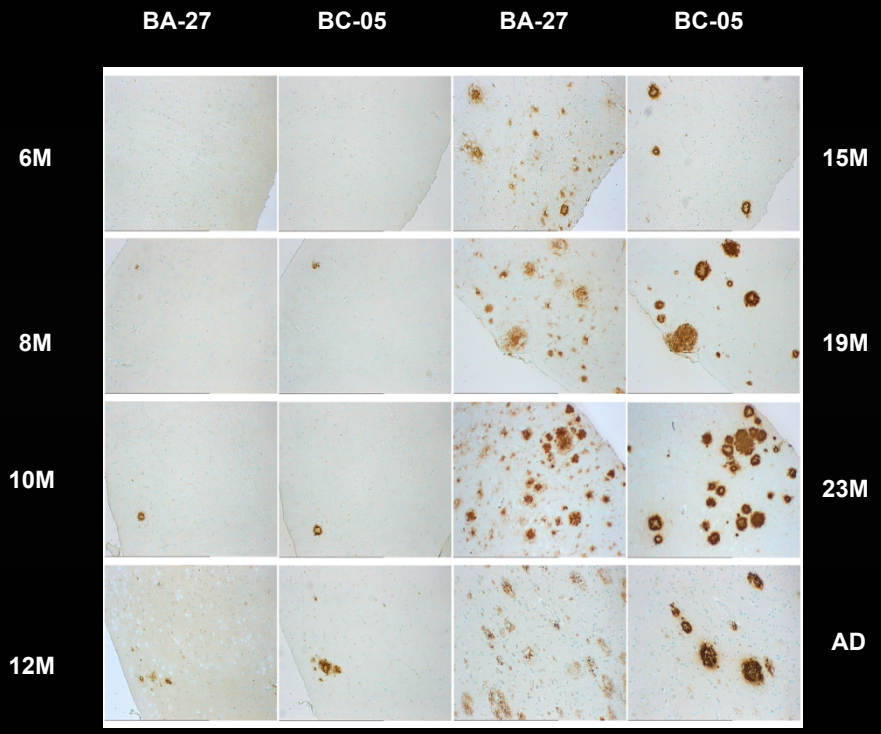
Brain Atrophy

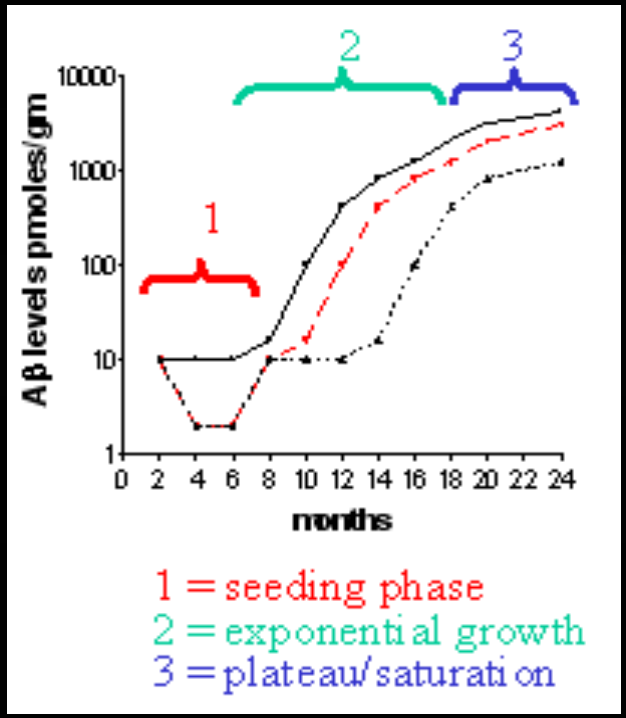


Neuronal Loss

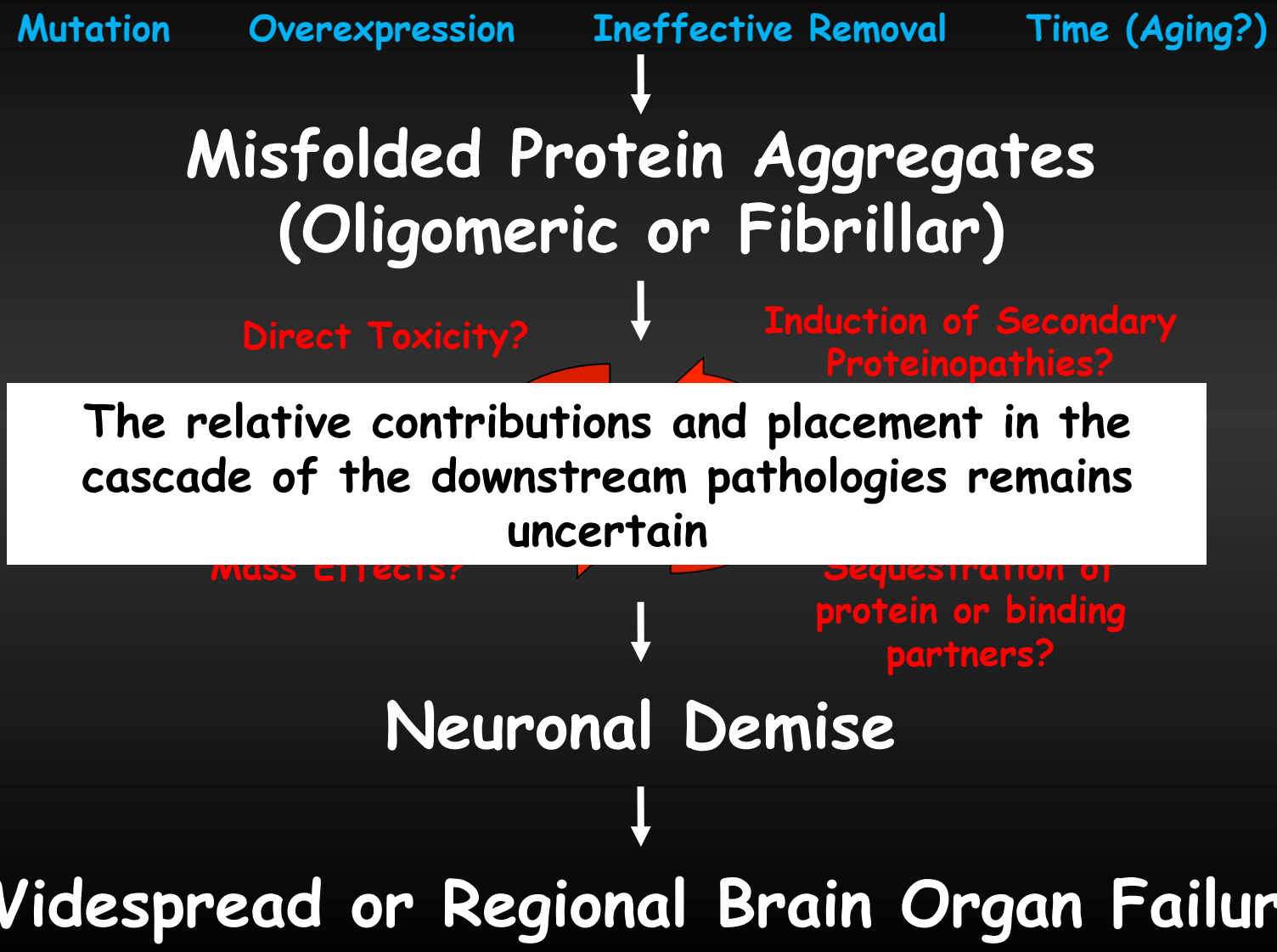
APP mice do not show massive neuronal loss or classic NFT pathology
Behavioral Phenotypes

We rarely conduct studies in APP mice that are reflective of human Aβ loads





Proteinopathies and Neurodegeneration



Ways Forward

- Can we solve the Treatment vs. Prevention Paradox?
  - We must collectively recognize the barriers to true primary prevention studies.
    - Financial: Public Private Partnerships, Change Patent Policy
    - Ethical
    - Regulatory/Legal
    - Safe Therapies