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?

• $\beta\mathrm{A}$ Aggregate Hypothesis:
  • $\beta\mathrm{A}$ 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

- FAD-linked APP mutations (chromosome 21)
- Trisomy 21/APP gene duplication
- More amyloidogenic Aβ
- FAD-linked Presenilin mutations (chromosome 14 and 1)

↑Aβ42
↑Aβ40 and Aβ42

APOE Clusterin SorL1 CR1

MAPT Mutations

Neurodegeneration

APOE
Clusterin
SorL1
CR1

MAPT
Mutations
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


- Provide additional strong support that accumulation of amyloidogenic peptides causes neurodegeneration

Rostango et al JBC 2002
Proteinopathies and Neurodegeneration

Mutation → Overexpression → Ineffective Removal → Time (Aging?) →

**Misfolded Protein Aggregates**
(Oligomeric or Fibrillar)

- Direct Toxicity?
- Innate Immune activation and Inflammation?
- Mass Effects?
- Induction of Secondary Proteinopathies?
- ROS, Mitochondrial Damage?
- Sequestration of protein or binding partners?

Neuronal Demise

Widespread or Regional Brain Organ Failure
A key assumption that underlies the Aβ aggregate hypothesis

• The fundamental 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)
Question #1

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

- $A\beta$ Aggregate Hypothesis:
  - $A\beta$ 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
    - 04-08-05. 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 $A\beta$: what's the magnitude of the problem

• In humans with AD ~10+ $\mu$moles of $A\beta$ accumulate (~100 mg).
  • = $A\beta$ produced in the brain in ~2-5 years.
  • During the deposition phase what percentage of $A\beta$ 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 $\mu$g) of $A\beta$ accumulate.
  • = $A\beta$ 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

α-Secretase Processing

- sAPPα
- CTFγ
- α-secretase activators
- Inhibitors of APP translation
- Cytoplasm

β-Secretase Processing

- APP
- Lumen
- CTFα
- β-secretase inhibitors
- CTFβ
- γ-secretase inhibitors

Aβ40
Aβ42
Selective Aβ42 lowering agent

P3
GSI studies using LY-411,575

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

<table>
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<tr>
<th>Compound</th>
<th>Mice</th>
<th>Route</th>
<th>Dose mg/kg/day</th>
<th>Length of Treatment</th>
<th>% A(\beta)40 Reduction Brain</th>
<th>% A(\beta)40 Reduction Plasma</th>
<th>Overt Toxicity</th>
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<tr>
<td>LY411575</td>
<td>Tg2576</td>
<td>Oral (Chow)</td>
<td>2.5</td>
<td>&gt;2 weeks</td>
<td>55%</td>
<td>74%</td>
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<td>5</td>
<td>&lt;2 weeks</td>
<td>77%</td>
<td>93%</td>
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*morbidity and mortality (skin lesions, bloating, intestinal bleeding, diarrhea)
“Window” therapy with a GSI (LY) (50% reduction in Aβ production)

Rx 4-7 months
Rx 7-10 months
Rx 12-15 months
And age to 15 months or longer

Begin GSI Rx in chow for 3 months

Onset of Detectable Aβ deposition 7.5-8 months

AD-like Aβ deposition 15+ months
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

Plaque quantification (% area)

Control

LY- dosed

4-7m

7-10m

12-15m

Earlier Rx Is More Efficacious at reducing Aβ Deposition

Plaque quantification (% area)
Conclusions: Initial Studies of GSI Window Therapy

- Early reductions in $A\beta$ provide a prolonged robust effect even after D/C of Rx
  - Exponentially more $A\beta$ 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 $A\beta$ production by >50%
  - Age not aging is critical
- Support Prophylactic rather than therapeutic targeting of $A\beta$ for AD
- NSAIDs, Statins, Estrogen etc all fail in therapeutic trials but epidemiology supports a protective effect
Caveats and thoughts

• Caveats:
  • CNS production of $\beta$ per unit time in mouse models is higher than 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?

Aβ deposition begins
Aβ deposition plateaus
CSF Aβ drops
Tau CSF rises

Optimal Prophylactic Rx

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, PhD¹

• 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

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.

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1 = seeding phase
2 = exponential growth
3 = plateau/saturation

Aβ levels pmol/gm
Proteinopathies and Neurodegeneration

Mutation  Overexpression  Ineffective Removal  Time (Aging?)

↓

Misfolded Protein Aggregates (Oligomeric or Fibrillar)

↓

Direct Toxicity?  Induction of Secondary Proteinopathies?

↓

The relative contributions and placement in the cascade of the downstream pathologies remains uncertain

↓

Mass Effects?  Sequestration of protein or binding partners?

↓

Neuronal Demise

↓

Widespread or Regional Brain Organ Failure
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