



An Australian Government Initiative

Prevention of cognitive decline and management of cognitive impairment



Collaborative partnerships • Translating evidence • Research partnerships

Professor Henry Brodaty & Katrin Seeher



Translating dementia research into practice



An Australian Government Initiative



Dementia Collaborative Research Centres

- **Assessment and Better Care (UNSW)**
- **Early Intervention, Prevention and Risk Reduction (ANU)**
- **Consumers, Carers and Social Research (QUT)**



An Australian Government Initiative



DCRC

Dementia Collaborative
Research Centres

National Dementia Research Forum

Translating Research into Practice

Australian Government Dementia: A Health Priority Initiative

18/19 Sept 2008 Sydney
www.dementia.unsw.edu.au

Translating dementia research into practice



An Australian Government Initiative



Conflicts of interest

- **Multiple - associations with every pharmaceutical company that has drugs for dementia in Australia**
- **Drug trials at Sydney Centre for Clinical Cognitive Research since 1989**
- **Referrals to Lynne 9382 3733**

lynne.seifman@sesiahs.health.nsw.gov.au



An Australian Government Initiative



DCRC

Dementia Collaborative
Research Centres



Estimated numbers of people with dementia worldwide, by year

Ferri CP, Prince M, et al;
Global prevalence of dementia:
a Delphi consensus study.
Lancet 2005; 366:2112-2117

24
million

2001

43
million

2020

81
million

2040

Ferri et al (2005). Lancet; 366: 2112-2117



Elimination vs Postponement

- **Disease elimination**
 - eg smallpox vaccination
 - best prospect is AD vaccine
- **Disease postponement (Brookmeyer R, 1998)**
 - delay AD onset by
 - 2 yrs \rightarrow \downarrow prevalence by 20%
 - 5 yrs \rightarrow \downarrow prevalence by 50%



Alzheimer's
Australia
Living with dementia





Dementia risk reduction signposts

MIND your DIET

MIND your BODY

MIND your BRAIN

MIND your HEALTH CHECKS

MIND your SOCIAL LIFE

MIND your HEAD

MIND your HABITS





An Australian Government Initiative



- ***Mind your Mind*** program from Alz Aus.
- **“What is good for your heart is good for your brain”**

Familiar, true but how true
.....how good is evidence?
.....how strong is the effect?



Smoking as a dementia risk factor



- **Smoking at baseline ¹:**
 - ↑ risk of dementia & AD if not ApoE4
- **Current vs. never smoker ²:**
 - ↑ risk for AD, VaD & any dementia
 - ↑ yearly decline in MMSE
- **Current vs. former smoker ²:**
 - ↑ risk for AD
 - ↑ decline in cog abilities
 - = in risk for VaD & any dementia

¹ Reitz et al (2007) Neurology; 69:998-1005

² Anstey et al (2007) Am J Epidemiology; 166:367-378

Alcohol and dementia^{1,2,3}



- **Not drinking in midlife¹**
 - ⇒ poorer performance in episodic memory, psychomotor speed, executive function
 - ⇒ Esp. among non-smokers
- **1-3 alcoholic drinks/day vs no alcohol**
 - ⇒ 45% ↓ risk of dementia in 8000 Ss followed for 8 yrs²
- **2-4 standard drinks/day**
 - ⇒ 50% ↓ risk of poorer cognition (MMSE<24) in men aged 80+ ³

¹ Ngandu et al (2007). Dem Geriat Cog Dis; 23:140-149; ²Ruitenbergh et al (2002). Lancet; 359:281-286; ³Flicker et al (2005). Age Aging; 34:77-80



Alcohol and dementia risk

- **Excessive alcohol consumption in midlife (=binge drinking once a mth)¹**
- **⇒ 3 fold increase in risk of dementia after age 65**
- **May be an interaction with ApoE4 status**
 - **E4 +ve, alcohol ? deleterious**
 - **E4 –ve, *moderate* alcohol may be protective**



¹ Jarvenpaa et al (2005) Epidemiology; 16:766-771



An Australian Government Initiative



DCRC
Dementia Collaborative
Research Centres



Caffeine and dementia

- **AD Ss drunk less coffee over past 20 yrs than controls ¹**
- **Having ≥ 3 cups vs ≤ 1 cup of coffee/day**
⇒ ↓ **cog decline over 4 yrs only in women ²**

¹Maia et al (2002) *Europ J Neurol*; 9:377-382;

²Ritchie et al (2007) *Neurology*; 69:536-545



An Australian Government Initiative



Poor nutrition and risk of cog impairment¹



- **33.8% of Ss were at moderate to high nutritional risk**
- **⇒ 71% higher risk of CI (MMSE \leq 17)**

¹ Lee et al (2007). Arch Geront Geriatrics`



An Australian Government Initiative



Fat intake and the risk of dementia

- Moderate vs low total fat and PUFA intake in midlife \Rightarrow about 60% \downarrow risk of dementia¹
- Saturated fat intake \Rightarrow 145% \uparrow risk of dementia (OR=2.45)¹
- \uparrow omega-3 fatty acids \Rightarrow \downarrow dementia risk²
- *But* recent literature shows limited evidence³
- *It's what fats you eat (eg Mediterranean diet)*

¹ Laitinen et al (2006). Dement Geriat Cogn Disord; 22:99-107; ²Kalmijn et al (2004).Neurol; 62:275-280; ³Issa et al (2006). Dem Geriat Cog Dis; 21:88-96



Cholesterol Hypothesis

- **Epidemiological studies → statins associated with ↓ risk of AD**
- **↑ levels of cholesterol may promote the production of A β through ↑ APP production**

Koudinov & Koudinov (2001)



Cholesterol and dementia risk

- **Hi midlife total cholesterol (TC) \Rightarrow \downarrow late life episodic memory and category fluency¹**
- **Moderate decrease (0.5-2mmol/L) \Rightarrow**
 - **\uparrow risk of $>$ impaired late-life cog status²**
 - **poorer late-life episodic memory¹ and psychomotor speed¹**
- **TC in AD Ss \downarrow \geq 15 yrs prior to diagnosis³**
- **Maybe indicator for early preclinical stage?³**

¹ Solomon et al (2007) Neurobiol Aging & ² Neurology; 68:751-756;

³ Stewart et al (2007). Arch Neur; 64:102-107

KS4

Sig. baseline difference in TC between control group and MCI group ($p < 0.001$) and between control group and dementia group ($p = 0.024$). No difference between MCI and dementia group ($p = 0.31$)

Late life assessment: differences no longer significant, i.e. general decrease of cholesterol over time in all groups

Katrin Seeher, 08/04/2008

Actions of statins

- **↓Cholesterol**
- **↓ LDL**
- **Anti-oxidant**
- **Anti-inflammatory**
- **Endothelial actions**
- **↓ A β in plasma and CSF in dose dependent**

Gandy S, 9 Jun 2007

Statins & AD: no effect¹



Heart Protection Study (N 20,536)

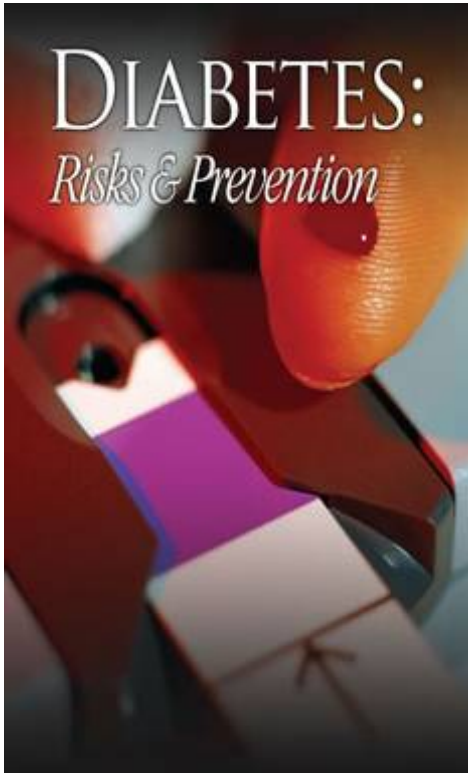
- 5 yr RCT: 40 mg/day simvastatin vs placebo
- Rx ↓ coronary death rate by 18% & non-fatal vascular events by 25%
- No difference between groups on incidence of dementia or cognitive impairment

Meta-analysis of preventative & Rx effects

- 7 studies – no significant benefit

¹Heart Protection Study Collaborative Group. *Lancet* 2002;360:7-22

² Zhou, B et al. (2007). *Dementia and Ger Cog Disorders*; 23:194-201



Diabetes as dementia risk factor

**Type 2 diabetes associated with ↑
risk of :**

- **Cognitive impairment**
- **Dementia**
- **Neuro-degeneration**

¹ Whitmer et al (2007). *Curr Neur Neuroscience Reports*; 7:373-380



Diabetes and risk of cognitive decline^{1,2}

- **40-50% higher rate of MCI in 918 Ss followed ≥ 1 yr¹**
- **Diabetes and hyperinsulinemia: ²**
 - **\uparrow risk of incident AD (HR=1.4)**
 - **\uparrow risk of incident dementia assoc with stroke (HR=1.9)**

¹ Luchsinger et al (2007) Arch Neurol; 64:570-575

¹ Muller et al (2007) Dem Geriat Cog Soc; 24:185-192



An Australian Government Initiative



Head injury and dementia risk

- **Significant discrepancies in literature re association between TBI, AD and APOE**
- **Trend that TBI is a potential risk factor for AD**
- **Role of ApoE remains inconclusive**

¹ Van Den Heuvel et al (2007) Prog Brain Research; 161:303-316



Head injury and dementia risk

- **Moderate to severe HI during World War II ⇒ 4.5 fold ↑ risk of AD and Dementia in general¹**
- **HI with loss of consciousness ⇒ 10-fold ↑ of AD risk²**
- **Rotterdam study could not find association between HI and risk of dementia³**

¹Plassman et al (2000). Neurology; 55:1158-66; ²Guo et al (2000). Neurology; 54:1316-23; ³Mehta et al (1999). Neurology; 53:1959-62



An Australian Government Initiative



Hypertension and dementia

- **Mid-life hypertension linked to stroke, heart disease, AD, MCI (all types, non-amnestic)**
- ***Decrease in systolic BP with age linked to AD***



Reitz et al (2007) Arch Neurol; 64:1734-1740

Li et al (2007). J Am Geriatr Soc; 55:1161-1167



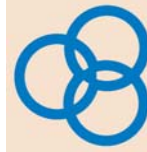
An Australian Government Initiative



Hypertension and dementia risk

- **Treatment for 12 yrs of hypertensive men from midlife reduced risk**
- **Each extra year of treatment ⇒ further reduction in risk of dementia**
- **60% ↓ risk of all dementia and AD**

¹ Peila et al (2006). Stroke; 37:1165-1170



Stroke and dementia risk¹

- **Stroke Ss had \uparrow risk of dementia (RR=3.7) and CI (RR=1.7)**
- **Esp. when < 75 yrs and ≥ 4 yrs education**
- **Dementia & CI prevalence in stroke Ss = prevalence in non-stroke Ss 10 yrs older!**
- **Sydney Stroke Study: of stroke patients 21% develop dementia within 1 year + 37% \rightarrow MCI ²**

¹ De Ronchi et al (2007). Dem Geriat Cog Dis;24:266-273

² Sachdev P et al, 2006 Dementia & Ger Cognitive Disorders. 21:275-83, 2006



Vit B₁₂, folate and dementia

- **Mixed findings for B12 and folate**
- **Homocysteine associated with higher rate of dementia, stroke and AD**
- **Folate can reduce homocysteine but no good evidence it decreases risk of AD**

¹ Clarke et al. (2007) J Clin Nutr; 86:1384-1391; ² Wang et al (2001) Neurology; 56:1188-1194; ³ Seshadri et al (2002). N Engl J Med; 356:476-483



Vit A, E & C and dementia risk reduction^{1,2}

- +**
 - Highest intake of vit E \Rightarrow 45% \downarrow risk of AD¹
 - Higher intake of vit C \Rightarrow also \downarrow risk¹
 - Heart protection study² did not find any benefit from Vit A, C and E intake
- - Vit E &/or Vit C \dashrightarrow risk of dementia or AD³
 - Meta-analysis, Vit E \rightarrow *higher* mortality rate⁴
 - Vit E may release free radicals⁵

¹ Engelhart et al 2002 JAMA; 287:3223-3229; ² ibid Lancet 2002; 360:23-33;

³ Gray et al (2008) J Am Geriatr Soc 56:291–295,



Vit B₁₂, Homocysteine, folate and dementia¹

- **Predictors of cog ↓ in 1648 Ss followed for 10 yr¹**
 - **↑tHcy: 2x ⇒ ≥ 50% more rapid decline**
- **Folate DID NOT predict cog decline¹**
- **↓ B₁₂ and folate ⇒ 2 times higher rates of AD²**
- **↑ homocysteine ⇒ double risk of AD³**

¹ Clarke et al. (2007) J Clin Nutr; 86:1384-1391; ² Wang et al (2001) Neurology; 56:1188-1194; ³ Seshadri et al (2002). N Engl J Med; 356:476-483



Folic acid, vitamin B₁₂ and dementia¹

- **High folate levels**
 - **↑ risk of CI for those with low B₁₂ level (OR=2.6)¹**
 - **↓ risk of CI for those w normal B₁₂ level (OR=0.4)¹**
- **RCT: folic acid (800 mcg) vs. placebo ²**
 - **Change in memory, information processing speed and sensorimotor speed**
 - **folic acid group sig. > placebo**

¹ Morris et al (2007). Am J Clin Nutr; 85:193-200; ² Durga et al (2007). Lancet; 369:208-216



An Australian Government Initiative



DCRC
Dementia Collaborative
Research Centres

Beta carotene and dementia ¹

- **N=4052 men aged 65+**
- **β carotene vs placebo**
- **Short-term (1yr) vs long-term (18yrs)**

Results:

- **No impact of short-term beta-carotene suppl.**
- **Long-term: beta carotene > placebo (for global cog score and verbal memory)**



¹ Grodstein et al (2007). Arch Int Med; 167:2184-2190



Protective activities when included in high levels of leisure activity

- Walking for pleasure or excursion
- Physical conditioning
- Cinema, restaurants, sporting venues
- Community/volunteer work
- Club or centres
- Church, synagogue, mosque attendance
- Visits to/from friends/ relatives
- Going to classes
- Reading magazines, newspapers and books
- Watching TV/ listening to radio
- Playing cards/ bingo
- Knitting, music, other hobbies

¹ Scarmeas et al (2001). *Neurology*; 57:2236-2242



Physical activity and dementia



- **Literature review¹:**
 - Trend for ↓ risk of cog decline in physically active elders
- **Causality?**
 - Does physical activity lower risk of dementia? or
 - Are those with better cog function and lower risk of dementia more likely to participate?

¹ Jedrziwski et al (2007). Alz Dem; 3:98-108

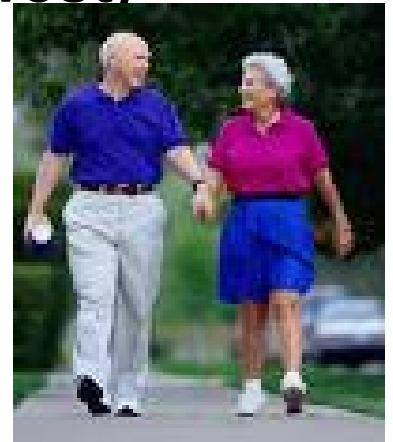


An Australian Government Initiative



Physical activity and dementia

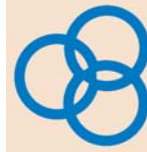
- 749 Ss aged 65+ followed for 3.9 yrs¹
- Risk ↓ only for VaD, not for AD
 - 73% for walking (upper tertiles vs. lowest)
 - 71% for moderate activities
 - 76% for total physical activity
- Physical exercise ≥ 3 times/week²
 - ⇒ 35% ↓ risk of dementia



¹Ravaglia et al (2007) Neurology; ²Larson et al (2006) Ann Intern Med; 144:73-81



An Australian Government Initiative



DCRC
Dementia Collaborative
Research Centres

Declining strength and AD risk¹



- 877 Ss without dementia
- Each 1-lb annual decline in grip strength \Rightarrow 9% \uparrow risk of AD
- controlled for relevant factors

¹ Buchman et al (2007). Neuroepidem; 29:66-73



An Australian Government Initiative



But, work-related physical activity ...

...was not associated with ↓ risk of dementia ¹

¹ Rovio et al (2007). Int J Geriat Psych; 22:874-882

- s16 only trends: physical active employees had increased risk of dementia (when education was considered onlu low educated group was on higher risk)
- commuting activity: sedentary group had lower risk for AD than moderate commuting group

sesahs, 04/04/2008



Level of Education and Dementia



- 6-8 yrs of education \Rightarrow 43% lower risk
 - ≥ 9 yrs of education \Rightarrow 84% lower risk
 - Controlled for demography, vascular variables, SES and lifestyle
-
- ✓ cognitive reserve
 - ✓ Unhealthy lifestyles independently contribute to dementia risk

¹ Ngandu et al (2007). Neurology; 69:1442-1450

s15

Association of education and AD risk was even stronger: 50% lower risk for medium education and 85% lower risk for high level education group
sesahs, 04/04/2008



An Australian Government Initiative



Cognitive activity and risk of AD¹

- > cog activity in 775 Ss followed for 5 yrs associated with:
 - ↓ incidence of AD (HR=0.58)
 - ↓ incidence of MCI (RR=0.71)
 - Less rapid decline in cog function



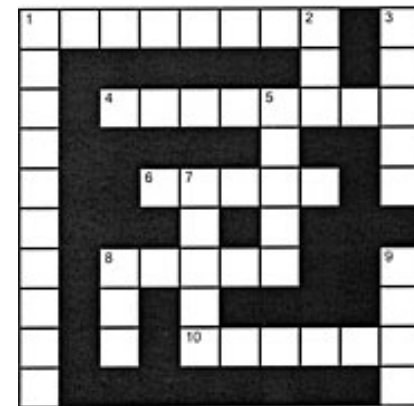
¹ Wilson et al (2007)
Neurology; 69:1911-20





Intellectual stimulation and dementia risk reduction

- **1-point \uparrow in activity-score (ranging from 0 to 5)**
 - \Rightarrow **47% lower risk of cog decline ¹**
 - \Rightarrow **33% reduced risk of AD ¹**
- **Mental, physical & social activities \downarrow dementia risk in Ss followed for 6yrs ²**
- **Combination \Rightarrow greatest benefit ²**
- **47% \downarrow dementia risk for high levels of ≥ 2 components²**



¹ Wilson et al (2002) JAMA; 287:742-748;

² Karp et al (2006) Dement Geriatr Cogn Disord; 21:65-73

s21 activities were listening to radio, reading, doing crosswords, visiting museums...
sesahs, 16/04/2008



An Australian Government Initiative



DCRC
Dementia Collaborative
Research Centres

Animal studies

- **Strongly support enhanced cognitive benefits associated with housing rodents in enriched environments**
 - include a combination of social, physical, and mental stimulation
 - compared with isolation

(Nithianantharajah & Hannan, 2006).



Cognitive training

- **Cognitive training ↑ memory & speed of progression in healthy elderly¹**
- **Type of training important for people who already have CI²**
 - **Memory < reasoning & speed training**
- **Booster sessions are necessary**

¹ IMPACT-Study, ²Unverzagt et al (2007) J Int Neuropsych Soc; 13:953-960 ACTIVE



An Australian Government Initiative



Cognitive training

- **Experimental trials: cognitive training can significantly improve performance in healthy adults on a range of cognitive tasks, with moderate effect size of 0.6**

Ball K et al, 2002 *JAMA*, 288, 2271-81

Willis et al 2006 *JAMA*, 296, 2805-2814

Mahncke, H et al, 2006 *Proc Nat Ac Sci, USA.*, 103, 12523-12528

Oswald W et al 2006 *Eur J Ageing*, 3, 179-192



Mental and physical activity

- **Cross sectional and prospective cohort studies consistently identify both**
 - **reduced risk of dementia and**
 - **reduced rate of cognitive decline**
- **In individuals who have engaged in**
 - **mentally and physically active pursuits**
 - **over their lifetime, or**
 - **even in late life**

(Valenzuela & Sachdev, 2006a,b,c)



Trials of exercise and older people

- **Acute exposure to just one bout of aerobic exercise can result in improved memory, attention, and reaction time**
- **Sustained improvements, particularly in executive function, relatively consistently after**
 - **aerobic training alone (ES=0.41)**
 - **combined aerobic and resistance training (ES=0.59) (Colcombe 2003) or**
 - **resistance training alone (ES=0.53)**



Loneliness and dementia risk¹

- **823 non-demented Ss followed for \leq 4 yrs, incl^u 90 who had died**
- **Loneliness \Rightarrow 51% \uparrow risk of late-life dementia**
- **41% \uparrow risk when controlled for cog activity**

¹ **Wilson et al (2007). Arch Gen Psych; 64:234-240**



Chronic distress and risk of MCI¹

- **1256 Ss without MCI followed for 12 yrs**
- **NEO-FFI's neuroticism scale = indicator for psych distress**
- **Risk of MCI ↑ by about 2% for each 1-unit increase on the distress scale**
- **Upper 10% were 42% more likely to develop MCI than the lowest 10%**

¹ Wilson et al (2007). *Neurology*; 68:2085-2092



Dementia risk in Australians:¹

- **2805 Ss, 14 yrs follow-up**
- **↑ hazard of dementia:**
 - **age**
 - **poor respiration**
 - **depression**
- **↓ hazard for dementia:**
 - **gardening daily (36%)**
 - **moderate alcohol intake (34%)**
 - **walking daily (only for men, 38%)**



¹ McCallum et al (2007) Ann NY Acad Sci; 1114:121-129



An Australian Government Initiative



Can risk reduction strategies prevent dementia in populations?

- \downarrow Risk factors \Rightarrow \uparrow survival in population
- *But* age is *the* main risk factor
- \Rightarrow little change in overall dementia risk

¹ Brayne (2007). Nat Rev Neuroscience, 8:233-239



Drugs for AD

4 drugs approved - all symptomatic:

- **Aricept (donepezil) - cholinesterase inhibitor**
- **Exelon (rivastigmine) - cholinesterase inhibitor**
- **Reminyl (galantamine) - cholinesterase inhibitor**
- **Ebixa (memantine) - NMDA receptor antagonist**



snowdrop bulb, an original source of Reminyl

Donepezil



- **Cochrane review**
 - 24 trials, 5796 participants
 - **Cognition: statistically significant improvement for both 5 and 10 mg/day of donepezil at 24 weeks v placebo on ADAS-Cog scale (-2.01 points MD, 95%CI -2.69 to -1.34, $P < 0.00001$)**
 - **Benefits on clinical global state, ADL and behaviour; but not on QoL**
 - **Controversy: cost v benefit**

Birks & Harvey (2006)



An Australian Government Initiative



DCRC
Dementia Collaborative
Research Centres

Developments with ChEIs

- Rivastigmine transdermal patch (Phase 4)
- Rivastigmine plus memantine (Phase 4)
- Donepezil SR 23mg (Phase 3)
- ZT-1 (Phase 2)



An Australian Government Initiative





Memantine (Ebixa)

- **NMDA antagonist, prevents excito-toxicity**
- **Approved for Moderate-Severe AD**
- **?Some cognitive benefits for 1st few months**
- **Symptomatic Rx**
- **Moderate to severe AD: 2 of 3 studies → small beneficial effect over 6m ¹**
- **Combined with donepezil > donepezil alone ²**

¹ R McShane, A Areosa Sastre, N Minakaran, *Cochrane Database of Systematic Reviews* 2007 Issue 1; ² Tariot P et al, *JAMA*. 2004;291:317-324.



An Australian Government Initiative



DCRC
Dementia Collaborative
Research Centres

New Strategies: Using the immune system



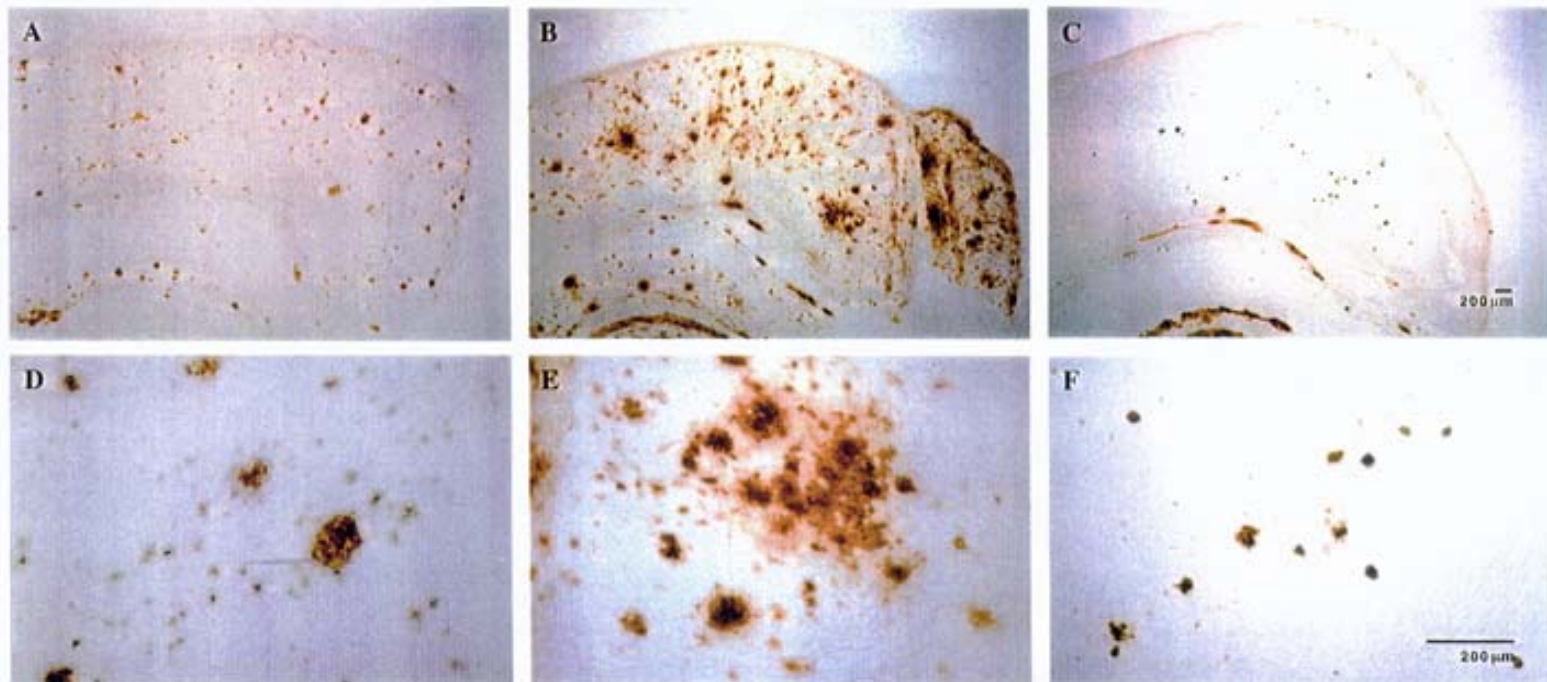
Immunisation & Protection from Amyloid Plaque

Schenk et al. FIGURE 4
TOP

12 Months

18 Months

18 Months immunized



¹Schenk D et al, Nature 1999;400:173-77



Active AD Immunisation¹

- **Trial stopped in phase II: 6% of subjects → meningo-encephalitis; some died**
- ***Head shrinkers: Brains of those with antibody response → smaller***
- **Some improvement in neuropsychological tests**

¹Solomon B, Expert Opinion on Biological Therapy, 2002

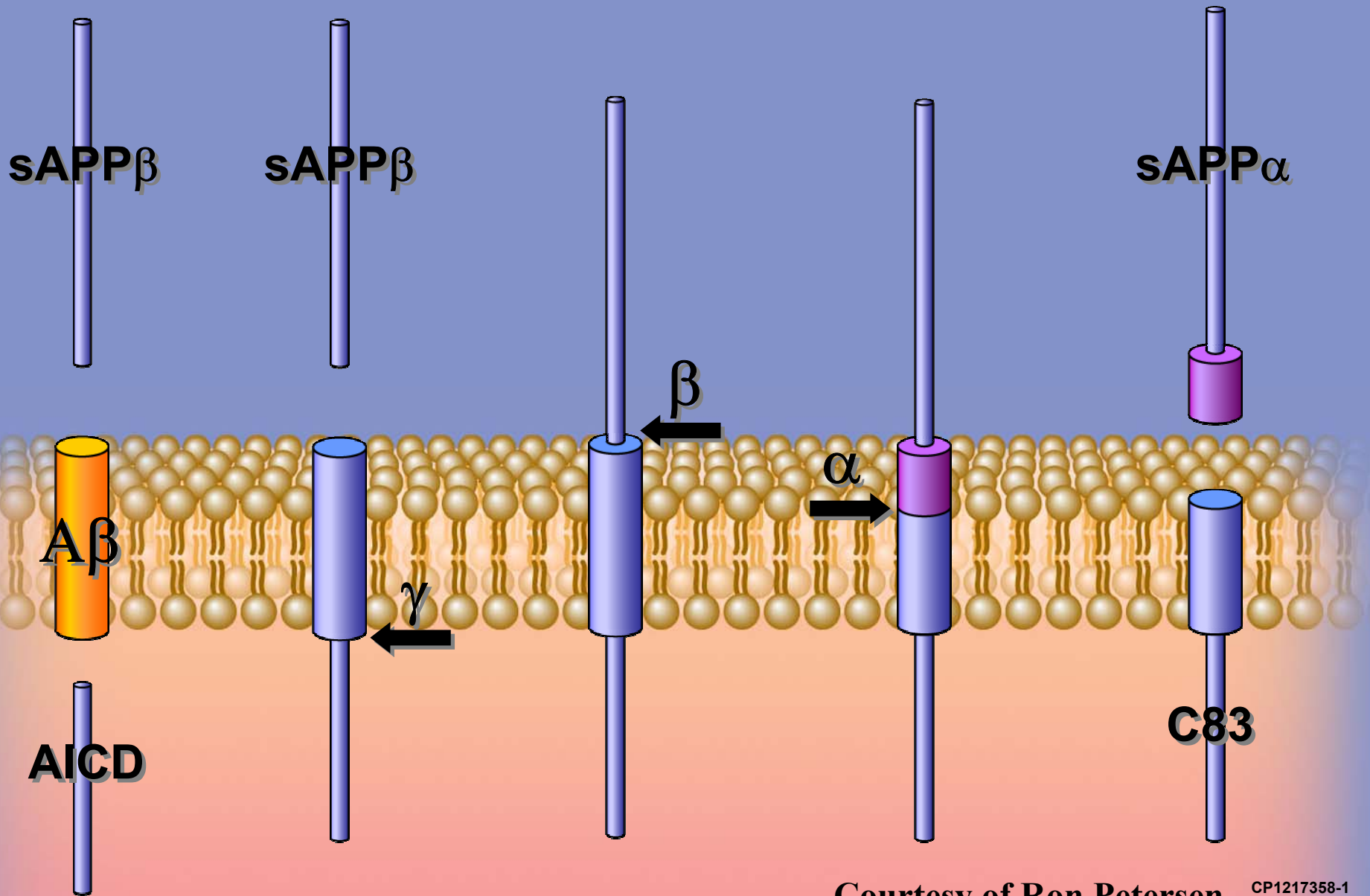


New immunisation Strategies

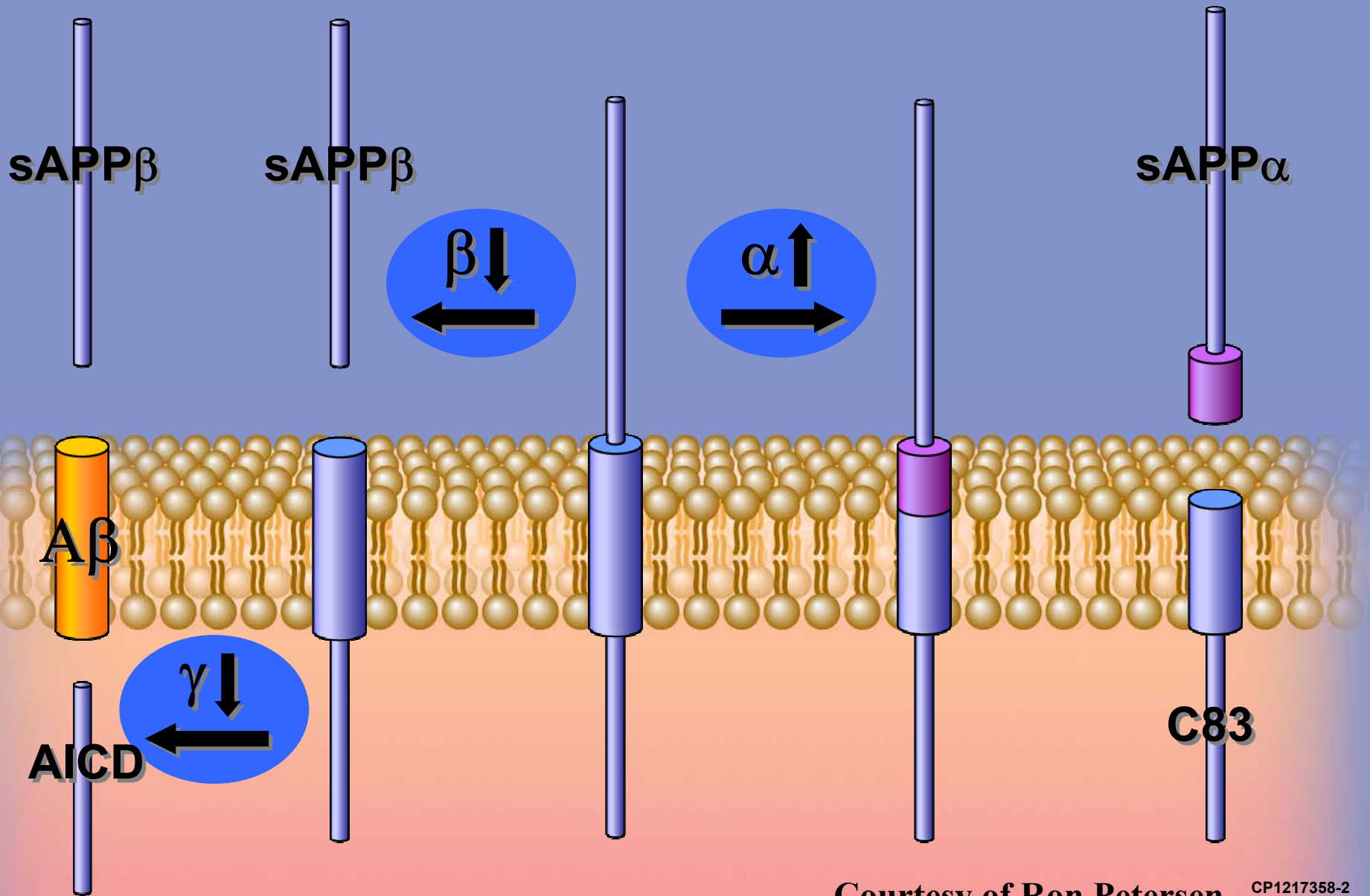
- **Active immunisation (antigen)**
 - **ACC-001 (Phase 2)**
- **Passive targeted immunisation (antibody)**
 - **AAB-001 (bapineuzumab) (Phase 2/3)**
- **Passive non-specific immunisation**
 - **Intravenous Immunoglobulin (Phase 2)**

¹**Solomon B, Expert Opinion on Biological Therapy, 2002**

Proteolytic Processing of APP Gives Rise to $A\beta$



Proteolytic Processing of APP Gives Rise to $A\beta$





Secretase strategies

- **γ Secretase inhibition**
 - **GSI-953 (Phase I)**
 - **LY450139 dihydrate (Phase II completed)**
 - **MPC-7869 (Phase III)**
- **β secretase inhibition**
 - **may be more successful in \downarrow amyloid deposition; no clinical testing yet**
- **α secretase augmentation**
 - **to reduce $A\beta$ release**



MPC-7869 (Flurizan) (Phase III)

- **Selective A β 42 lowering agent (SALA) (also anti-inflammatory; flurbiprofen)**
- **↓ γ -secretase & ↓ A β 42 by ~ 70% (nonclinical studies)**
- **Phase II trial: AD patients who took 800 mg of Flurizan BD for 12 mths had less deterioration: ADLs = 48% (p<0.05), CDR-sb = 36% (p<0.05); but not ADAS-Cog = 34% (NS)**

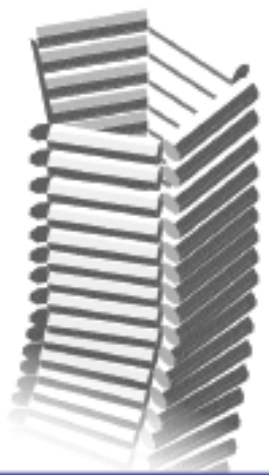
Morihara et al. (2002). *J Neurochem*;83:1009-12;

Eriksen et al. (2003). *J Clin Invest*;112:440-9; <http://www.myriad.com/alzheimers/flurizan.php>

Free A-beta peptide

Free-floating fibril

Amyloid plaque



Zn/Cu

Monomer

Oligomer

Protofibril

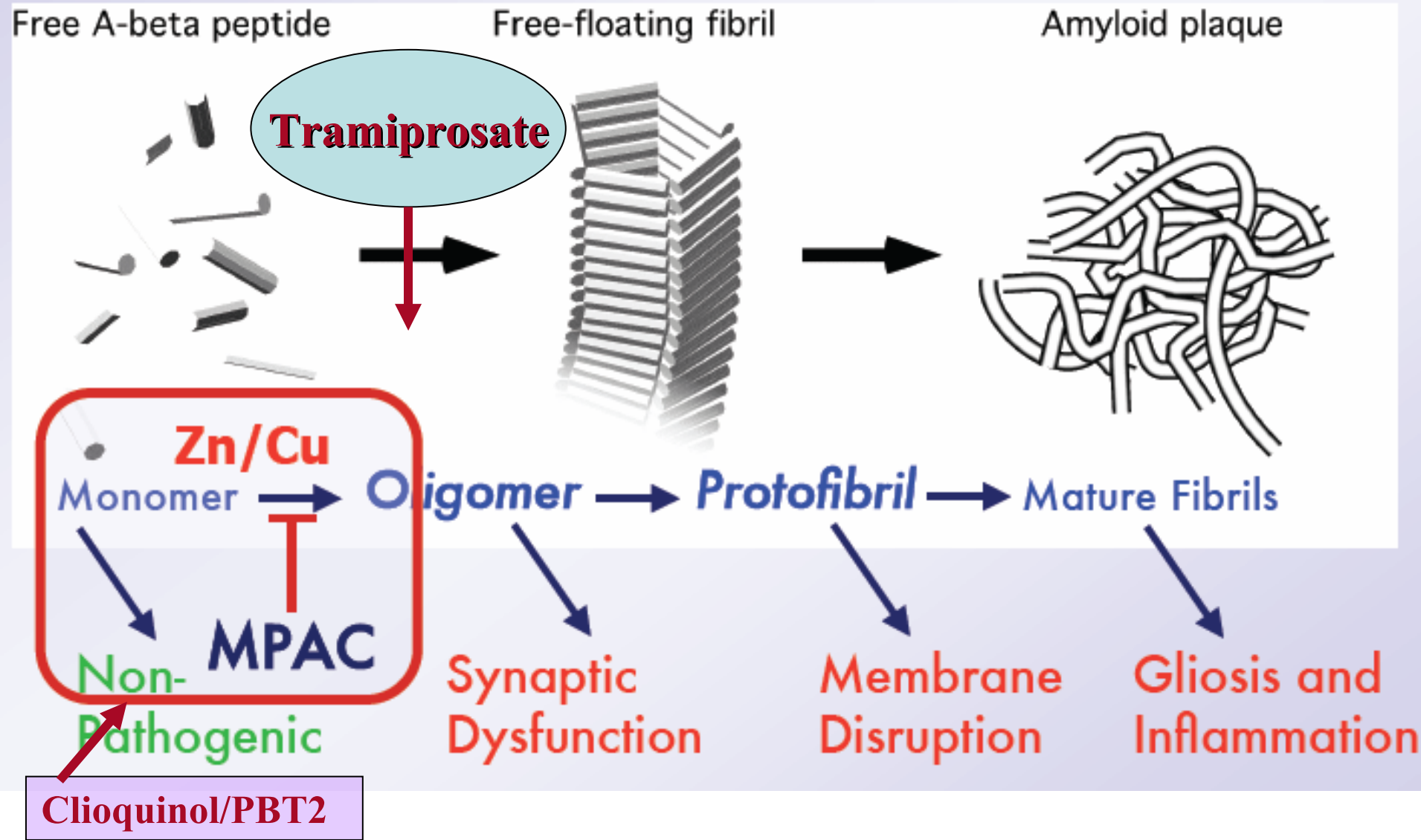
Mature Fibrils

Non-Pathogenic

Synaptic Dysfunction

Membrane Disruption

Gliosis and Inflammation





Tramiprosate (Alzhemed; 3APS) (Phase III)

- **A glycosaminoglycan (GAG) mimetic**
- **Binds to A β**
- **Phase 3 trial, USA, completed**
- **Stabilises cognition especially mild AD**
- **Recent trial possibly negative**
- **Other inhibitors of A β aggregation:**
 - **PPI-1019 (APAN) (Phase 1/2 completed)**
 - **TTP488 (Phase 2 completed)**

Aisen, P CNS Drugs 2005; Aisen, Neurology 2006; Aisen, in DC 2007



Metal Chelating Agents

- **Zinc & copper are required for the oligomerisation of A β protein**
- **Oligomers result in Amyloid plaques**
- **Clioquinol or PBT1 (terminated) and ...**
- **PBT2 (Phase 2/3); pilot \rightarrow positive results**
- **target zinc & copper in brain to prevent formation of toxic A β oligomers**



Rosiglitazone

- Prelim results show some \uparrow in APOE4 negative vs APOE4 positive subjects
- RSG may be effective in a genetically defined subset of patients with mild-moderate AD
- Recent meta-analysis found increased risk of myocardial infarction¹

¹Nissen & Wolski (2007). N Engl J Med; 356:2457-2471



Dimebon (Phase II)

- Long used in Russia as antihistamine
- Inhibitor of cholinesterase and NMDA receptors
- Inhibits neuronal death, potentially by mitochondrial-mediated inhibition of apoptosis
- RCT 183 AD patients; improvement in ADAS-Cog, CIBIC-plus, MMSE, NPI & ADLs at 26 wks compared to placebo; strong effects
- Russian trial, well supervised; need replication

Alzheimer Research Forum, <http://www.alzforum.org/drg/drc/default.asp>;
Doody et al. (2007). AA Int Conference on Prevention of Dementia



Ginkgo Biloba: Rationale

- **Increases blood supply by dilating blood vessels**
- **Reduces blood viscosity**
- **Modifies neurotransmitter systems**
- **Anti-oxidant**
- **Anti-inflammatory properties**

Birks et al (2007). Cochrane Database of Systematic Reviews



Ginkgo Trials

- **EGb 761 (Tanakan) (Phase II/IV):**
standardised extract of Ginkgo biloba leaves
- **Trials for prevention**
 - **GEM**
 - **GuidAge**



Rationale

- **Curcumin = active ingredient**
- **metal chelator**
- **antioxidant**
- **anti-inflammatory & COX-I**

Trials

- **Curcumin & Ginkgo extract
(Phase I/2)**
- **Curcumin C3 Complex
(Phase 2)**

Turmeric^{1,2}



Member of ginger family

¹Ringman JM et al, Current Alz Research; ²Zhang H-Y, Science Direct 2005



Turmeric Trials

- **Curcumin and Ginkgo extract (Phase I/2)**
- **Curcumin C3 Complex (Phase 2)**



- Important in neurogenesis
- supplementation in mice
→ ↓ amyloid pathology

Trials of DHA

- DHA (Phase 3)
- Fish oil and alpha lipoic acid (Phase 1/2)
- EPAX 1050TG: fatty acid composition rich in DHA

DHA





Turmeric

Natural therapies

- **Great interest and research in traditional and herbal therapies**
- **Especially in China and Asian countries**



Conclusion - Prevention

- **Healthy diet, avoid obesity**
- **Active lifestyle – cognitive, physical, social**
- **Attend to BP, cholesterol**
- **Don't smoke, alcohol in moderation**
- **Food rich in anti-oxidants, polyphenols**



Conclusion – Management of cognitive impairment

- **Current medications are symptomatic**
- **New medications on horizon may halt or prevent Alzheimer's disease**
- **Active physical, mental and social life**
- **Cognitive training limited benefit**

Thank you
h.brodaty@unsw.edu.au



An Australian Government Initiative



DCRC

Dementia Collaborative
Research Centres

National Dementia Research Forum

Translating Research into Practice

Australian Government Dementia: A Health Priority Initiative

18/19 Sept 2008 Sydney
www.dementia.unsw.edu.au

Translating dementia research into practice