

Promoting the Health of Canada's Seniors



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Overview

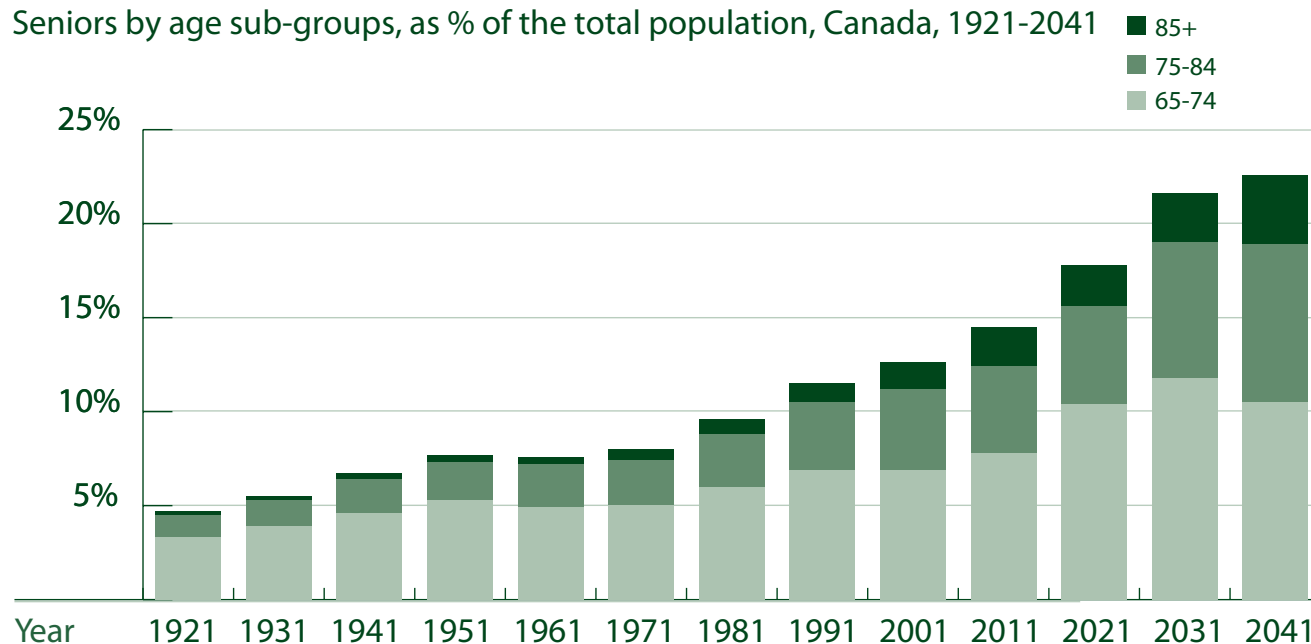
- What does Canada's aging population look like?
- What are the major health care concerns for this group?
- How can we best support health and vitality for Canadian seniors?

Seniors in Canada

- In 2001, one in eight Canadians was over 65 years. By 2026, one in five Canadians will be 65 years or older.

Chart 1

Seniors by age sub-groups, as % of the total population, Canada, 1921-2041



Common Diseases of Aging

- Cardiovascular disease
- Cancer
- Diabetes
- Pulmonary disease
- Arthritis
- Incontinence
- Osteoporosis
- Depression
- Dementia

Health care economics and aging

Health care is costing Canada over \$170 billion per year, with approximately 70% of the costs incurred by seniors.

The Current Challenge

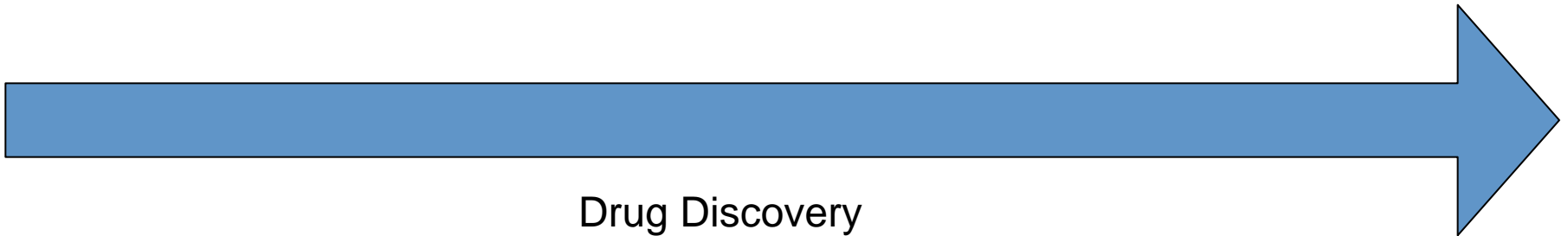
- How do we distribute the efforts to care for our seniors now, promote healthy aging in the current population, and treat or prevent diseases of aging in the future?

Research and Discovery

Preclinical Development

Clinical Trials

Policy development/Standard of Care



Alzheimer's Disease?



Alzheimer's disease is an irreversible, progressive brain disease that slowly destroys memory and thinking skills.

Clinical features include a progressive memory loss, language deterioration, disorientation, impaired judgment, inability to perform everyday tasks, and personality changes.

Alzheimer's Disease is the most common cause of senile dementia, and affects approximately 50% of the population over 85 years of age.

In 2006, the global burden of AD was 26.6M. By 2050, this will quadruple to over 100M, which is roughly one in 85 persons.

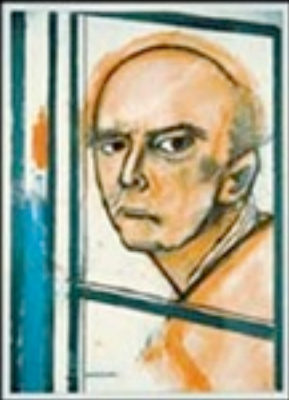
Grace

An acclaimed documentary film on Alzheimer's Disease

[http://www.youtube.com/watch?
v=7wbYEK7O14Ext](http://www.youtube.com/watch?v=7wbYEK7O14Ext)

The impact of Alzheimer's Disease

1996



1997



1997



1998



1999



2000



Six self-portraits by artist William Utermohlen chronicle his experience with Alzheimer's disease.

He was diagnosed at the age of 60 years, just after the first self-portrait was completed.

What causes Alzheimer's Disease?

AD is not a part of normal aging. It is a fatal disease that affects the brain.

Only 5% of AD is caused by genetic mutations that lead to early onset AD typically between 40-55 years of age. These mutations all cause increased production of A β peptides, which are thought to trigger the onset of AD.

Over 95% of AD patients have sporadic AD. The biggest risk factor for AD is age, and most people develop AD after 60 years of age. A leading current theory is that the ability to remove A β peptides declines with age.

Modifiable Risk Factors for Alzheimer's Disease

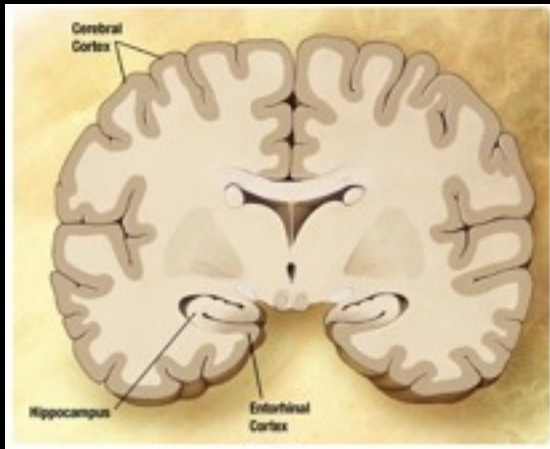
Table 1: Risk factors for Alzheimer disease

Factor	Risk (95% CI)
Systolic hypertension > 160 mm/Hg	RR: 1.5 (1.0-2.3) ⁴ OR: 2.3 (1.0-5.5) ⁵
Serum cholesterol > 6.5 mmol/L	RR: 2.1 (1.0-4.4) ⁵ RR: 3.1 (1.2-8.5) ⁶
Moderate wine consumption (250-500 mL/d) compared with more or less than this amount	RR: 0.53 (0.3-0.95) ⁷
High level of physical activity* compared with little or no regular exercise	RR: 0.5 (0.28-0.90) ⁸ RR: 0.55 (0.34-0.88) ⁹ RR: 0.69 (0.5-0.96) ¹⁰
Smoking, current	RR: 1.74 (1.21-2.50) ¹¹ RR: 1.99 (1.33-2.98) ¹²
Head injury, with loss of consciousness	
Moderate	HR: 2.32 (1.04-5.1) ¹³
Severe	HR: 4.51(1.77-11.47) ¹³
Education > 15 yr (v. < 12 yr)	RR: 0.48 (0.27-0.84) ¹⁴
Statin drugs	RR: 0.82 (0.46-1.46) ¹⁵ HR: 1.19 (0.35-2.96) ¹⁶
Nonsteroidal anti-inflammatory drugs	RR: 0.42 (0.26-0.66) ¹⁷ RR: 0.51 (0.37-0.70) ¹⁸

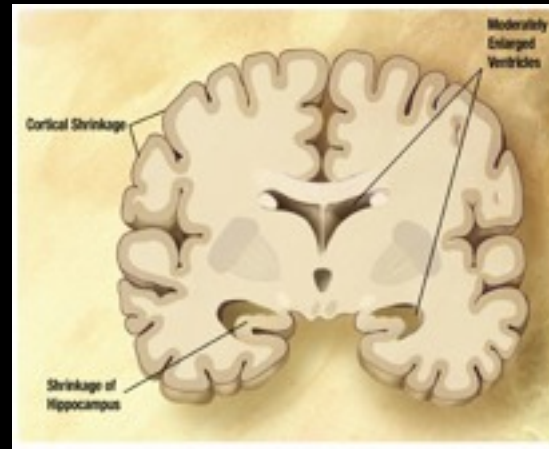
Patterson et al (2008)
CMAJ 178: 548-556

The Changing Brain in Alzheimer's Disease

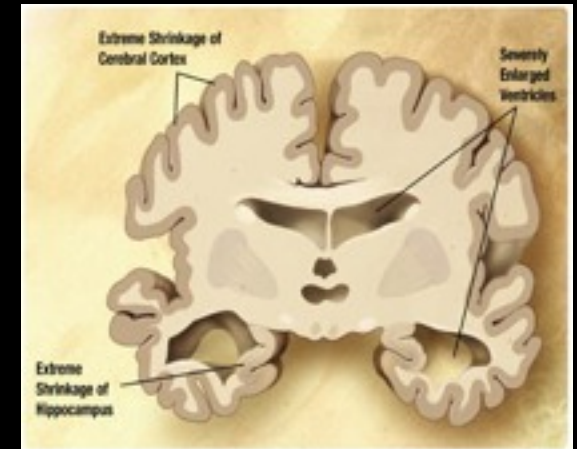
Preclinical AD



Moderate AD

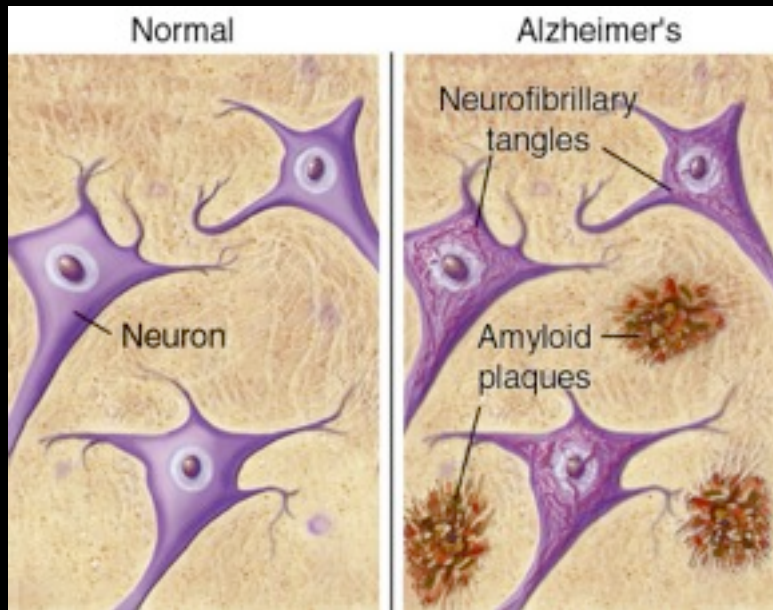


Severe AD

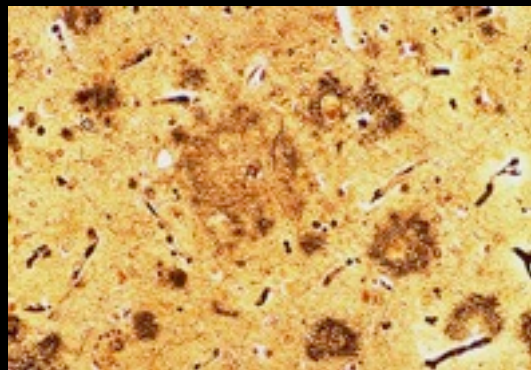
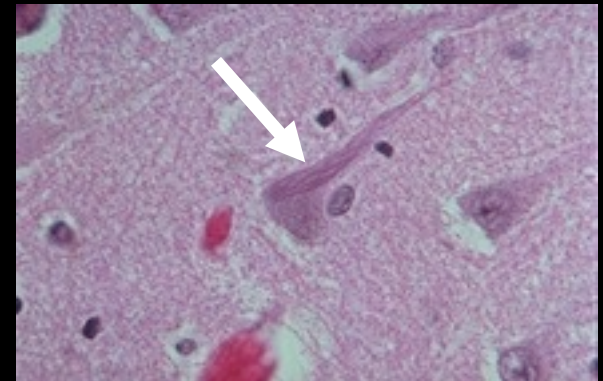


AD results in progressive loss of grey matter starting in the limbic system and extending to the cortex.

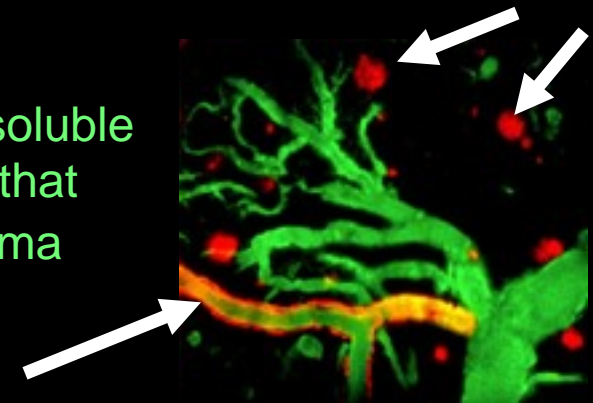
How Alzheimer's Disease is diagnosed



Neurofibrillary tangles are composed of intern neuronal hyperphosphorylated tau aggregated in a paired helical structure



Amyloid plaques consist of insoluble $A\beta$ peptides, apoE, and lipids that are deposited in the parenchyma and cerebral vessels



A horizon of hope for Alzheimer's Disease

Much current research focuses on understanding the key underlying mechanisms of Alzheimer's Disease to reveal potential new therapeutic or preventative approaches for this devastating disease. These include:

- Halting the production of A β peptides
- Promoting the clearance of A β peptides

- Understanding how inflammation, oxidation, and cerebrovascular factors contribute to Alzheimer's Disease

The Wellington laboratory



Study the interrelationships between Alzheimer's Disease and metabolism

Investigate genes that regulate apoE and cholesterol metabolism in the brain

Study their impact on Alzheimer's Disease in cell culture and in animal models

The Brain Research Centre and the Centre for Brain Health have been critical for this work



Apolipoprotein E is a genetic risk factor for late-onset Alzheimer's disease

Gene Dose of Apolipoprotein E Type 4 Allele and the Risk of Alzheimer's Disease in Late Onset Families

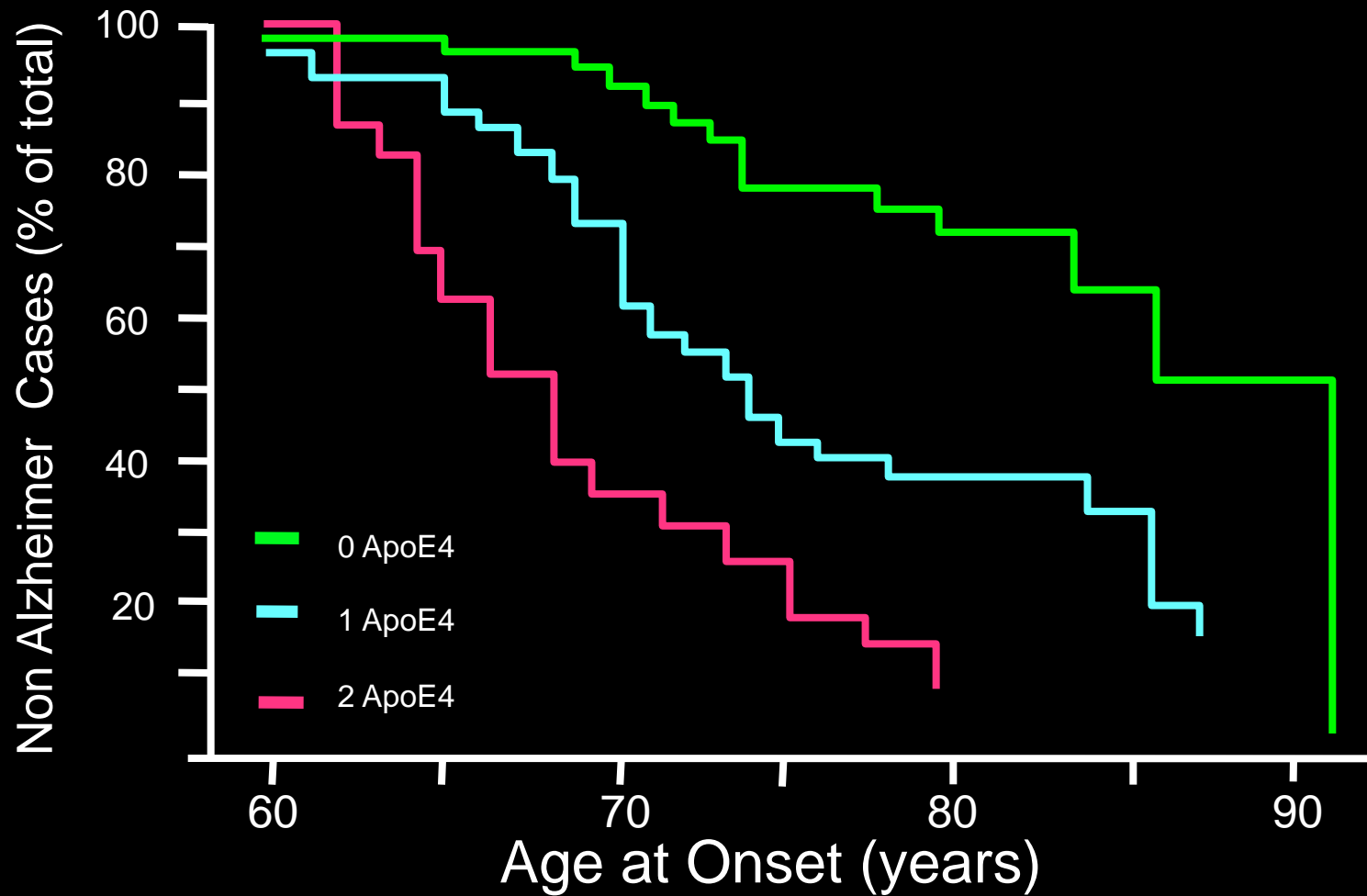
E. H. Corder, A. M. Saunders, W. J. Strittmatter, D. E. Schmechel, P. C. Gaskell, G. W. Small, A. D. Roses, J. L. Haines, M. A. Pericak-Vance*

The apolipoprotein E type 4 allele (*APOE-ε4*) is genetically associated with the common late onset familial and sporadic forms of Alzheimer's disease (AD). Risk for AD increased from 20% to 90% and mean age at onset decreased from 84 to 68 years with increasing number of *APOE-ε4* alleles in 42 families with late onset AD. Thus *APOE-ε4* gene dose is a major risk factor for late onset AD and, in these families, homozygosity for *APOE-ε4* was virtually sufficient to cause AD by age 80.

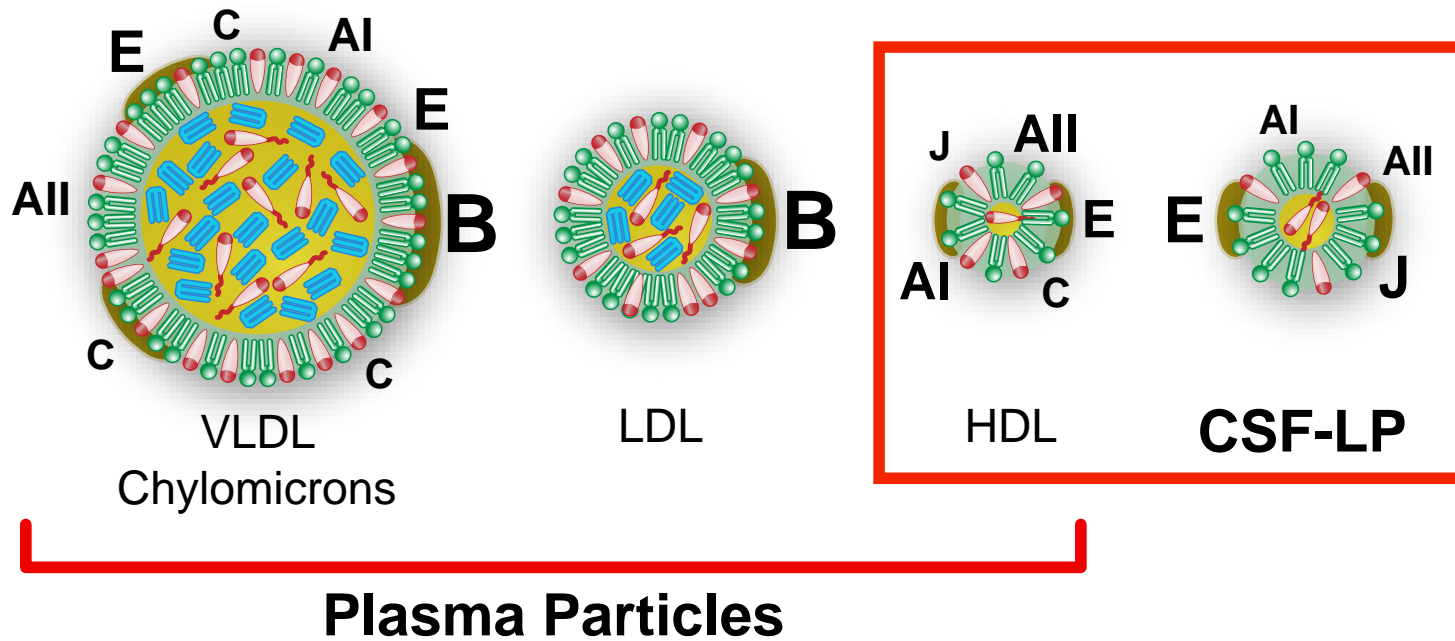
Three major alleles of apoE affect the risk of Alzheimer's disease

Allele	Amino Acids	Prevalence	Effect on AD
apoE2	Cys112, Cys158	7%	delays onset
apoE3	Cys112, Arg158	78%	normal allele
apoE4	Arg112, Arg158	15%	accelerates onset

ApoE4 Decreases the Age of Onset of AD



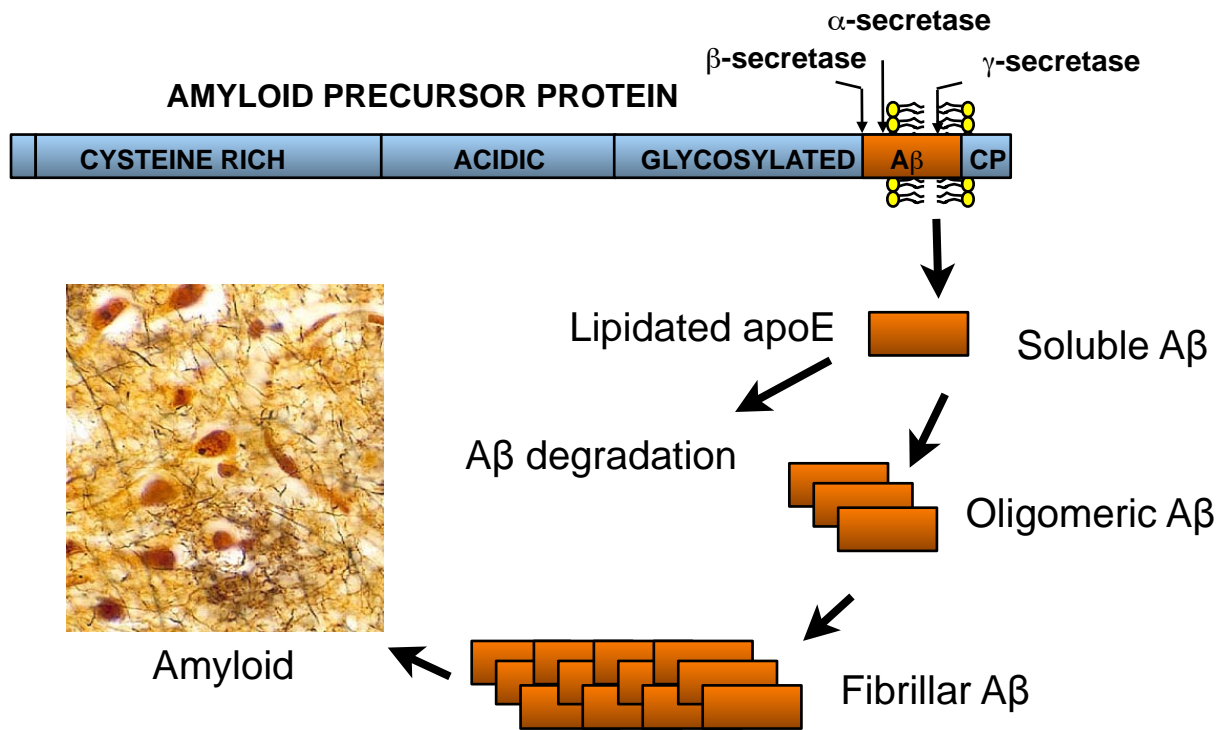
Fats in the brain are carried on apoE



Discoveries from the Wellington lab

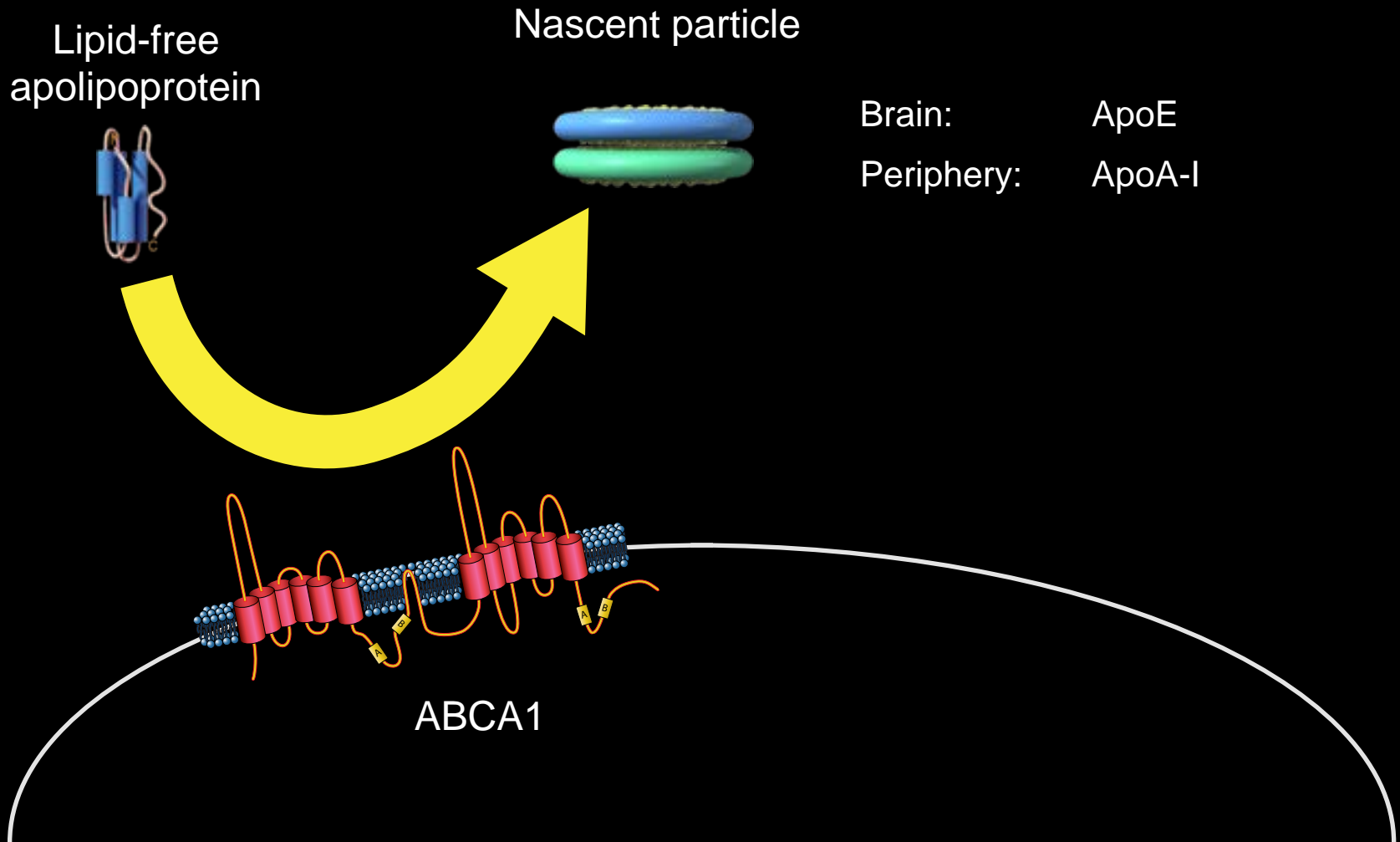
- Current research shows that how much cholesterol is on apoE is key determinant of amyloid burden
- ABCA1 is the protein that moves cholesterol onto apoE in the brain
- ABCA1 activity therefore influences amyloid burden in mouse models of AD
- Drugs that stimulate the ABCA1-apoE pathway may be of potential interest for AD

How we think apoE may work in AD



apoE “greases the wheels” to remove Aβ from the brain

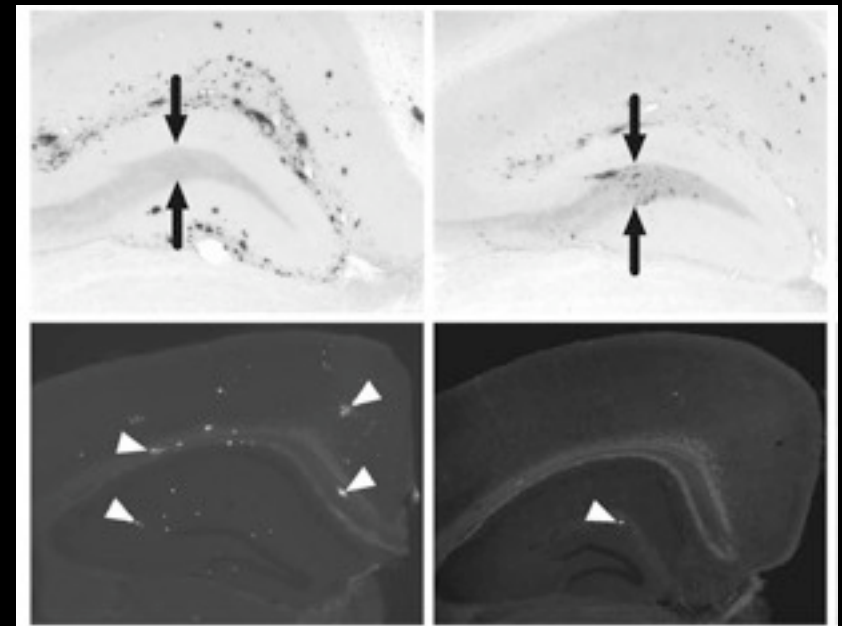
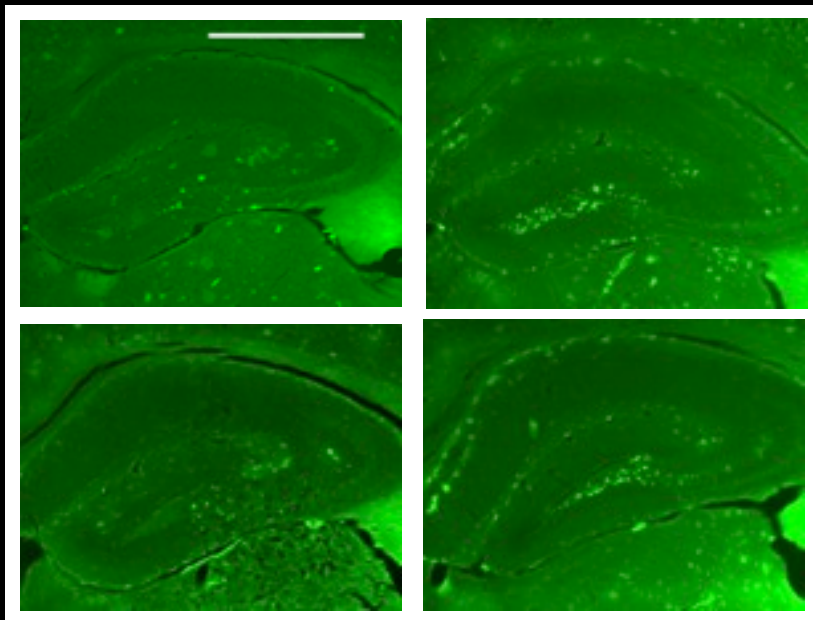
The cholesterol transporter ABCA1 adds lipids to apolipoproteins during cholesterol efflux



ABCA1 levels regulate amyloid load in AD mice

ABCA1^{-/-} mice have increased amyloid

ABCA1 Tg mice have decreased amyloid



ABCA1
+/+

ABCA1
-/-

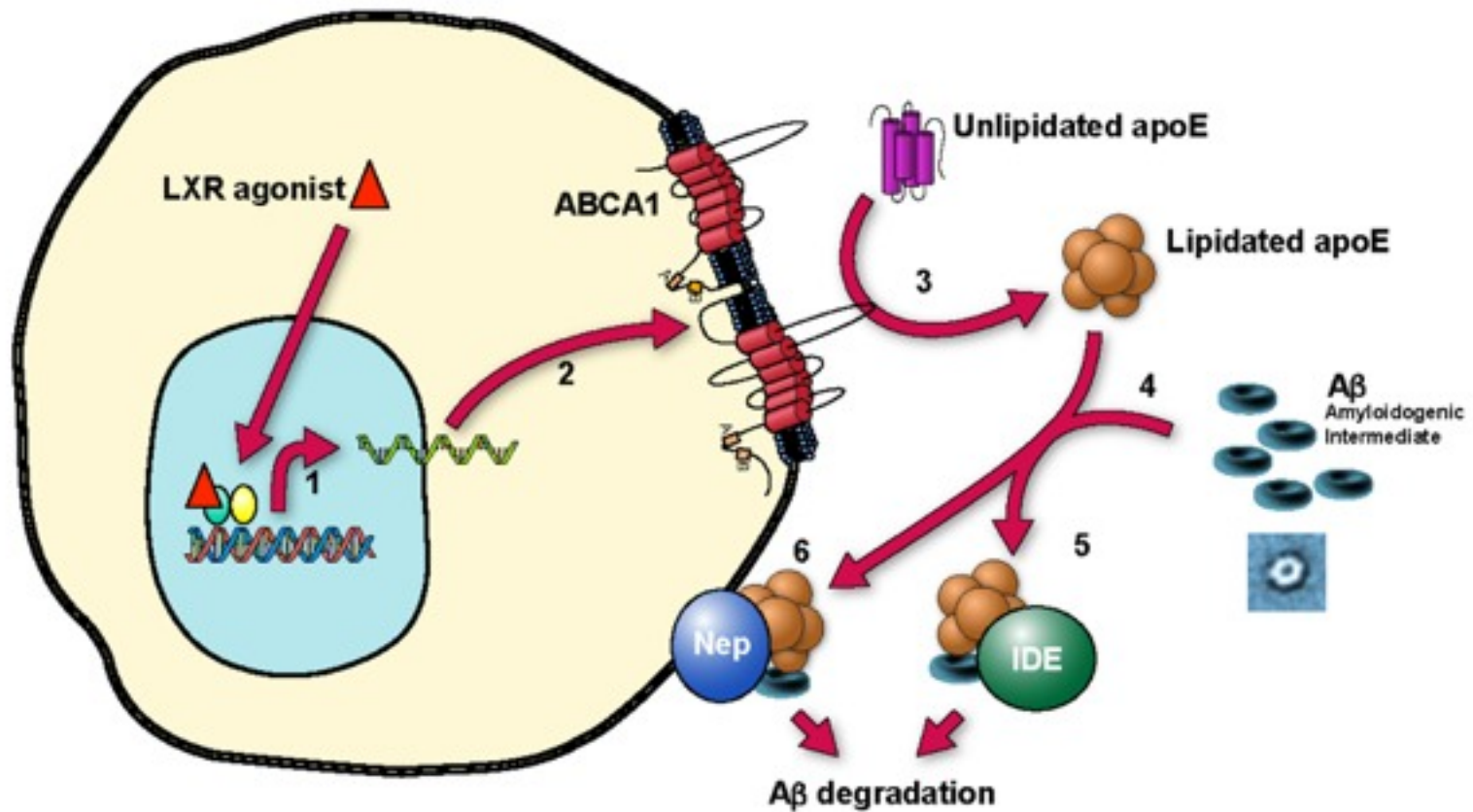
ABCA1
+/+

ABCA1
Tg

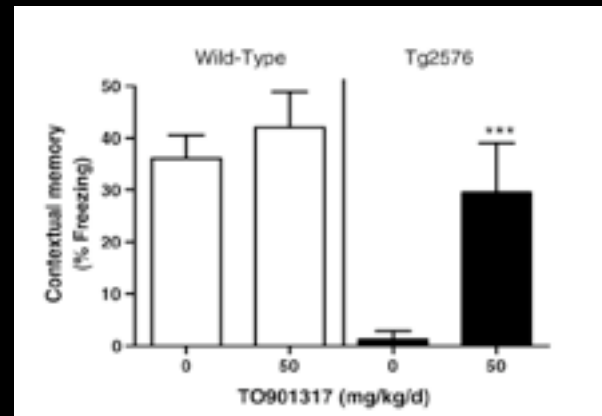
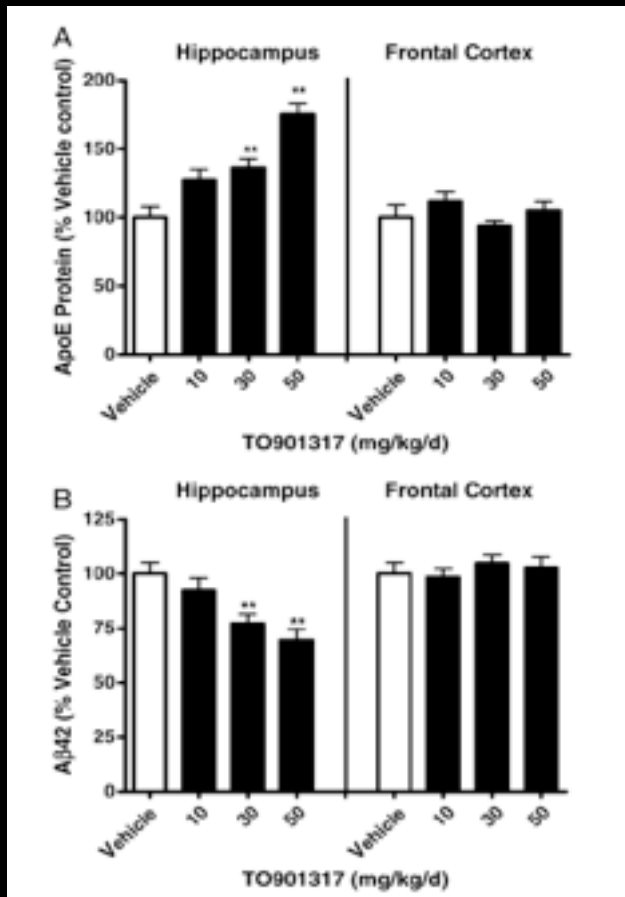
Poorly lipidated apoE is detrimental

Highly lipidated apoE is protective

The ABCA1-apoE pathway and A β clearance



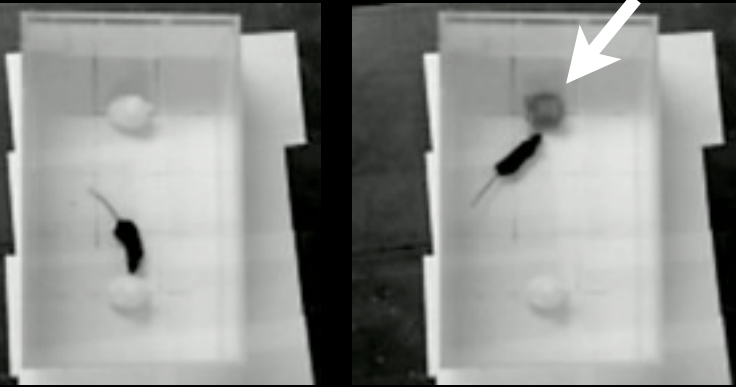
LXR agonists reduce A β and improve memory in AD mice



- Symptomatic Tg2576 mice were treated with TO901317 for 7 days
- Treated mice showed a selective reduction in hippocampal A β 42 levels
- TO901317 treatment reverses the deficit in contextual fear conditioning

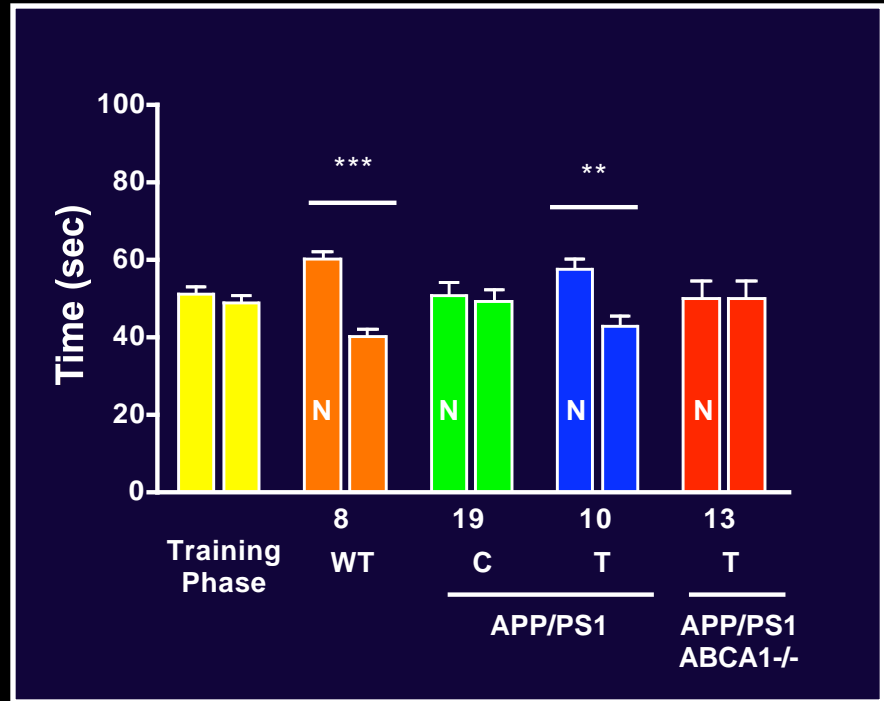
ABCA1 is necessary for the restoration of novel object recognition in GW3965 - treated AD mice

Novel Object



Training Phase

Testing Phase



To recap:

- ABCA1 adds lipids to apoE in the brain
- In mice, removing ABCA1 makes AD worse, whereas augmenting ABCA1 activity prevents AD
- Drugs known as LXR agonists enhance ABCA1 activity and effectively treat AD in mice
- ABCA1 is crucial for the beneficial effects of LXR agonists

The problem

- Despite a multimillion dollar effort by the pharmaceutical industry, no existing LXR agonist is safe for use in humans
- All existing LXR agonists will induce hepatic steatosis (fatty liver)
- This undesirable side effect means the therapeutic potential of the ABCA1-apoE pathway has remained untapped

The solution

- Together, Dr. Michael Oda and Dr. Cheryl Wellington have developed a novel approach to capitalize on the therapeutic potential of the ABCA1-apoE pathway for AD
- Their strategy is to sidestep the insurmountable side effects of LXR agonists by directly applying the beneficial *products* of the ABCA1-apoE reaction, namely brain HDL, as therapeutic agents for AD



The finances

- Generation and testing of over 30 formulations for biocompatibility, A β clearance, and lipoprotein function • \$750,000
- Optimization of formulations for BBB transit and route of administration • \$500,000
- Efficacy testing in AD mouse models • \$650,000

We need to raise at least \$1.9M
for this research program

Acknowledgements

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Brain Research Centre

Centre for Brain Health

Child and Family Research Institute

Canadian Institutes of Health Research

Alzheimer's Society of Canada/AstraZeneca

Pacific Alzheimer's Research Foundation

Alzheimer's Drug Discovery Foundation

The Brain Research Centre

The Brain Research Centre includes more than 200 investigators across several fields of neuroscience research:

- synaptic function and plasticity
- neurodegeneration
- multiple sclerosis
- mental health and addiction
- stroke
- neurotrauma
- vision
- pain
- neuroethics

Key technologies include **imaging** and **genomics**

Key themes include **the learning brain** and **the aging brain**

The BRC is expanding to include translational and clinical research as the Centre for Brain Health

Your support is critical to launching and maintaining internationally recognized research programs at UBC

THANK YOU!



Rendering of the proposed Centre for Brain Health