New Drugs in Alzheimer's Disease

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Research & Enterprise

From This ….

Daily Mail

MONDAY, SEPTEMBER 7, 2009 www.dailymail.co.uk 50p

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Genetic scientists reveal biggest breakthrough for 15 years

ALZHEIMER'S: A MASSIVE LEAP

By Fiona MacRae
Science Reporter

BRITISH scientists have made the biggest breakthrough for more than 15 years in the fight against Alzheimer's.

Their landmark research could revolutionise the understanding of a condition that blights the lives of 400,000 Britons and their families.

It could cut the rate of new cases by a fifth – up to 100,000 a year in the UK.

British and French teams have identified eight genes responsible for one in five cases of the disease. The search is now on for drugs to combat them.

The research has also raised the possibility that Alzheimer's may be caused by inflammation of the brain. This means anti-inflammatory medicines already in common use, including aspirin and ibuprofen, could help ward off or even treat Alzheimer's.

Rebecca Wood, of the Alzheimer's Research Trust, said: 'These findings are a leap forward for dementia research.

'At a time when we have yet to find ways of halting this devastating condition, the development is likely to spark off numerous new ideas and conference in the race for a cure.'

In the biggest study of its kind, a British-led team of more than 50 scientists scanned the DNA of some 14,000 people from eight countries, including 4,000 Alzheimer's patients. This flagged up two genes – clusterin and PICALM – that raise the risk of the disease if they

Turn to Page 2

Lord Freddie Windsor and actress Sophie Winkleman, who will marry on Saturday

ROYAL BRIDE'S BOMBSHELL

SEE PAGE THREE

Barnardo's chief: Take babies from bad parents

By Steve Doughty
Social Affairs Correspondent

BABIES born to feckless parents should be taken away as soon as possible for adoption, the head of a leading children's charity said yesterday.

Barnardo's chief Martin Narey said social workers should no longer waste time 'fixing families that can't be fixed'.

His extraordinary plea goes against the official stance that families should be kept together if at all possible.

'If you can take a baby very young and get them quickly into a permanent adoptive home, then we know that in most we have success,' Mr Narey said.

His comments – which he admitted would be seen as an 'illiberal heresy' – were instantly dismissed by Children's Secretary Ed Balls.

FULL STORY: Page 6

The Independent, 7 September, 2009

… And This ….

5p CHEAPER THAN THE DAILY MAIL AND TEN TIMES BETTER

DAILY EXPRESS

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BURIED ALIVE: COUPLE FOUND DEAD IN CAR TEN DAYS AFTER LANDSLIDE

SEE PAGE 5

VICTIM: Rosemary Snell

BRITAIN'S ECONOMY BOOSTED AT LAST

SEE PAGE 2

PILL TO BEAT ALZHEIMER'S

New treatment will stop disease for three years

By Giles Sheldrick

ALZHEIMER'S sufferers and their devastated families were last night given new hope after scientists hailed the "most exciting" breakthrough yet in the search for a cure.

A drug has been shown to stop the harrowing disease in its tracks for three years – whereas current treatments only slow down the symptoms.

Trials of the drug, known as immunoglobulin, have proved so successful it could be available at chemists in pill form within a decade.

Excited

The findings were revealed yesterday at the Alzheimer's Association International Conference in Vancouver, Canada. The world's largest gathering of dementia researchers was said to have been left stunned.

One leading scientist told the Daily Express: "This type of treatment is a new approach.

"Previously licensed drugs have only been able to slow the progression of symptoms whereas this drug harnesses the body's immune system to tackle the underlying cause of the disease. The reason that everyone is getting very excited about this is because it's the most

TURN TO PAGE 4

The Duchess of Cambridge's name has been added to William and Harry's Royal Foundation SEE PAGE 9

KATE, WILLS AND HARRY'S PRINCELY SUM FOR CHARITY

University of Sussex

Daily Express, 18 July, 2012

… To This ….

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INDEPENDENT

Drug giants give up on Alzheimer's cure

Research too difficult and costly, say pharmaceutical companies

By **JEREMY LAURANCE**
Health Editor

The world's leading pharmaceutical companies are downgrading the search for new treatments for Alzheimer's disease after the failure of a series of high-profile drugs trials.

The human and financial costs of the disease are growing rapidly as the population ages, but the prospects of treatments to halt it, or slow its progress, are receding as at least five trials in the past five years have delivered disappointing results.

This year, a trial of Dimebon, backed by Pfizer, the US pharmaceutical giant, and reported in January, failed to show any benefit, instead costing the company $750m in lost investment.

In July, bapineuzumab, developed by Irish drug-maker Elan in association with Pfizer and the US multinational Johnson & Johnson, also failed to show an impact on symptoms.

In August, another US group, Eli Lilly, reported the failure of solanezumab, its second Alzheimer's drug to disappoint in two years. In 2010, a trial of semagacestat not only failed to slow the disease but worsened symptoms.

The setbacks have damaged confidence among drug makers in the field of neuroscience – brain research – which was already shaky.

Pharmaceutical manufacturers worldwide are under pressure and have been cutting back in the recession, but neuroscience has been disproportionately hit, with AstraZeneca, Pfizer, Merck, Sanofi, Novartis and GlaxoSmithKline all downsizing

Continued on **PAGE 6**

Capita to be paid bounty for catching illegal immigrants

By **NIGEL MORRIS**
Deputy Political Editor

Ministers were accused last night of placing a "bounty" on illegal immigrants' heads after the UK Border Agency announced that a private company will be brought in to track down more than 170,000 people still in the country after their visas expired.

Capita will be paid up to £30m on a payment-by-results basis.

Full report, **PAGE 15**

The Independent, 19 September, 2012

Where are we now?

- Current medications for Alzheimer's Disease are only modestly effective
- Recent data (summer '12) on big clinical trials on two drugs, Bapineuzumab and Solanezumab, were disappointing
- Our understanding of Alzheimer's disease has advanced hugely over the last 30 years
  - Translating our understanding into new drugs remains the challenge

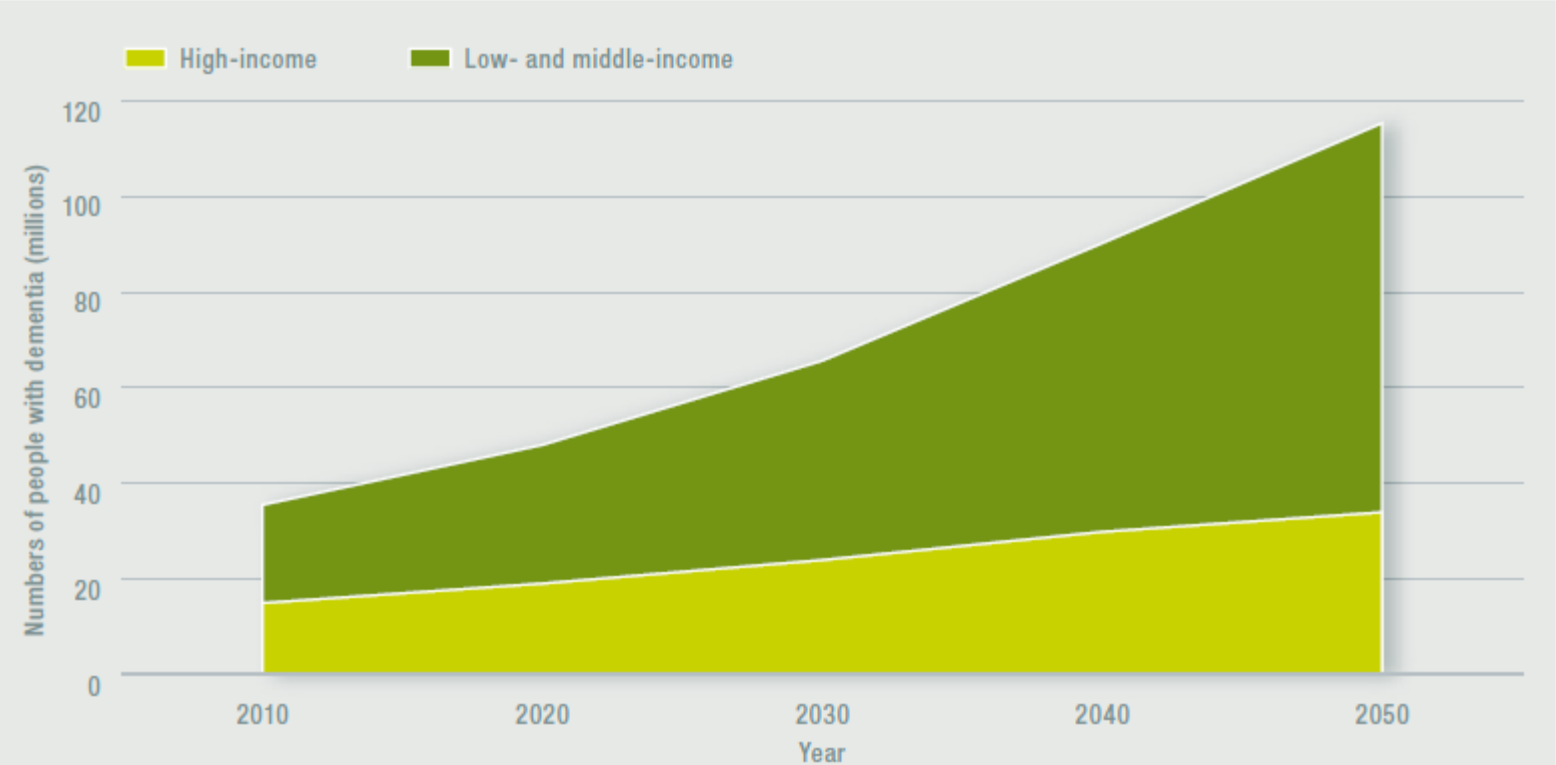
Outline of Presentation

- Introduction to Alzheimer's Disease
- The Drug Discovery Process
- Current Drugs for Alzheimer's Disease
- Amyloid-related drugs for Alzheimer's Disease
  - Segamacestat
  - Bapineuzumab, Solanezumab
- What happens next?

Alzheimer's is the Most Common Form of Dementia

Cause	Occurrence %
Alzheimer's disease (AD)	57
Vascular dementia (VD)	13
Depression	4.5
Alcohol	4.2
Normal pressure hydrocephalus	1.6
Metabolic and medications	3.0
Neoplasm	1.5
Parkinson's disease	1.2
Huntington's disease	0.9
Mixed AD and VD	0.8
Infection	0.6
Subdural hematoma	0.4
Post-trauma	0.4
Other	7.1
Not demented	3.7

Alzheimer's Disease – A Growing Problem

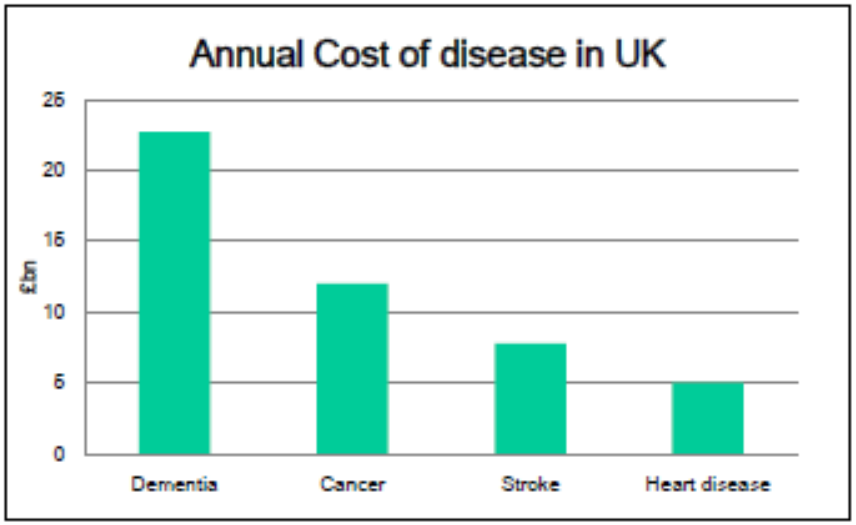


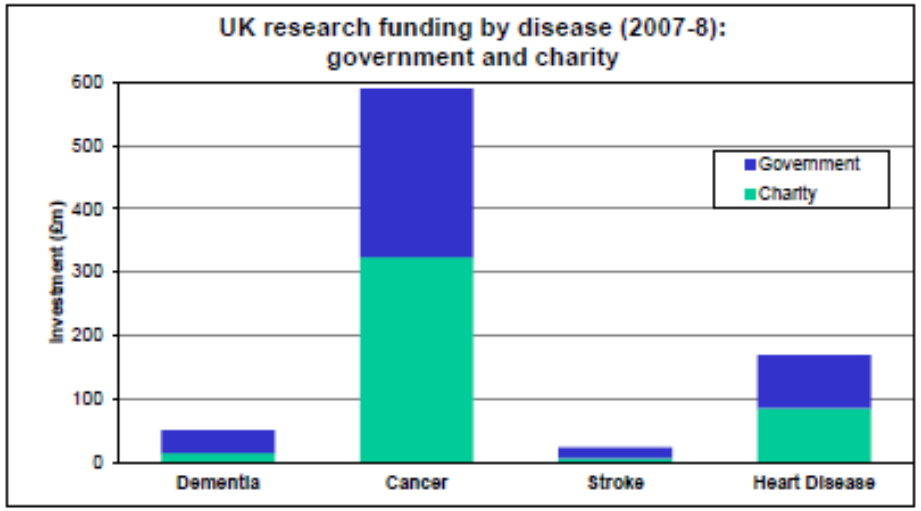
Slide courtesy of Eric Karran,
Scientific Director, Alzheimer's Research UK

WHO/Alzheimer's Disease International 2012

University of Sussex

Alzheimer's Disease Costs – 2007-8 Figures

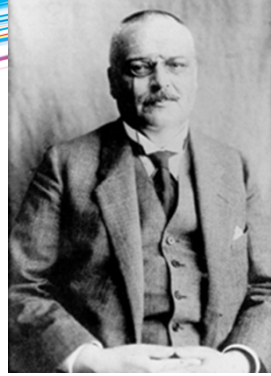




Slide courtesy of Eric Karran, Scientific Director, Alzheimer's Research, UK

"At least 12 times as much was spent on cancer research as dementia research, yet dementia cost the country twice as much as cancer"

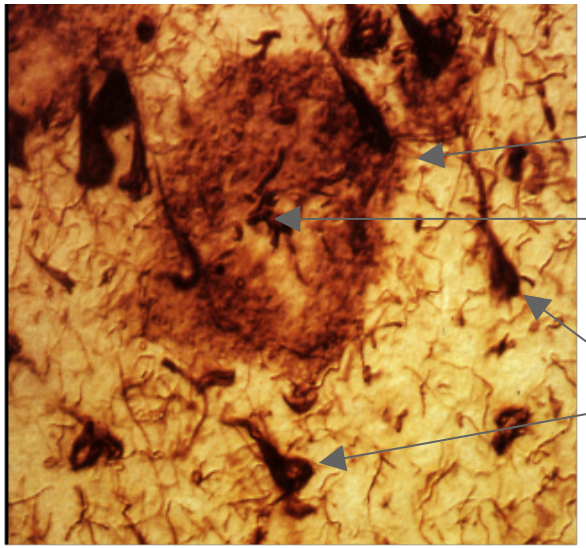
E. Karran, The Independent, 19th September, 2012



Amyloid and Alzheimer's Disease

Auguste D. (age 51) admitted in to an asylum in 1901 due to "delerium and frenzied jealousy of her husband"

Alzheimer attempted to relate clinical symptoms to pathological changes (1906)



Alzheimer's Disease – A Brief History

1906 Alzheimer's first description of Alzheimer's Disease

1968-1970 dementia not merely due to hardening of the arteries

1976 reduced levels of acetylcholine neurotransmission demonstrated

1984 composition of amyloid protein identified

1991 a gene associated with Alzheimer's Disease identified

- This and other genes are involved with the production of amyloid
- The "amyloid hypothesis" has dominated recent therapeutic strategies

1993 ApoE identified as a risk factor

2009 Additional (small) AD risk factors identified

2012 APP mutation reported to be afford protection against AD

Diagnosis of Alzheimer's Disease

1. Diagnose dementia
2. Rule out others possible causes of dementia
   - Possible AD (atypical clinical features, no other cause, no histology)
   - Probable AD (typical clinical features without histology)
   - Definite AD (clinical diagnosis with histological confirmation)

Typical clinical features

- Memory impairment
- Loss of language
- Visuospatial deficits (e.g. drawing)
- Motor and sensory abnormalities, gait disturbances only in latter stages
- Duration can vary from 2-3 years to 15-20 years

Measuring Disease Severity

- There are a variety of tests of cognitive function
  - Alzheimer's Disease Assessment Scale – Cognition subscale (ADAS-Cog)
  - Blessed dementia rating scale
  - Cambridge Neuropsychological Test Automated Battery (CANTAB)
  - Mini-mental state exam (MMSE)
  - Neuropsychiatric Inventory (NPI)

- Activities of daily living ratings scales
  - Disability Assessment for Dementia (DAD)
  - Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL)
  - ADCS-Clinical Global Impression of Change (ADCS-CGIS)

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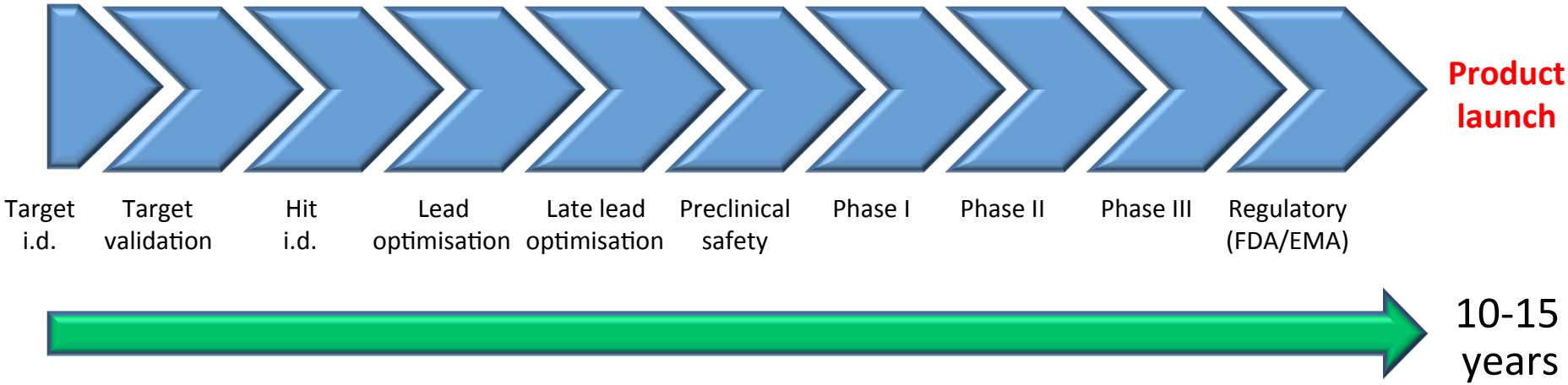
The Drug Discovery Process

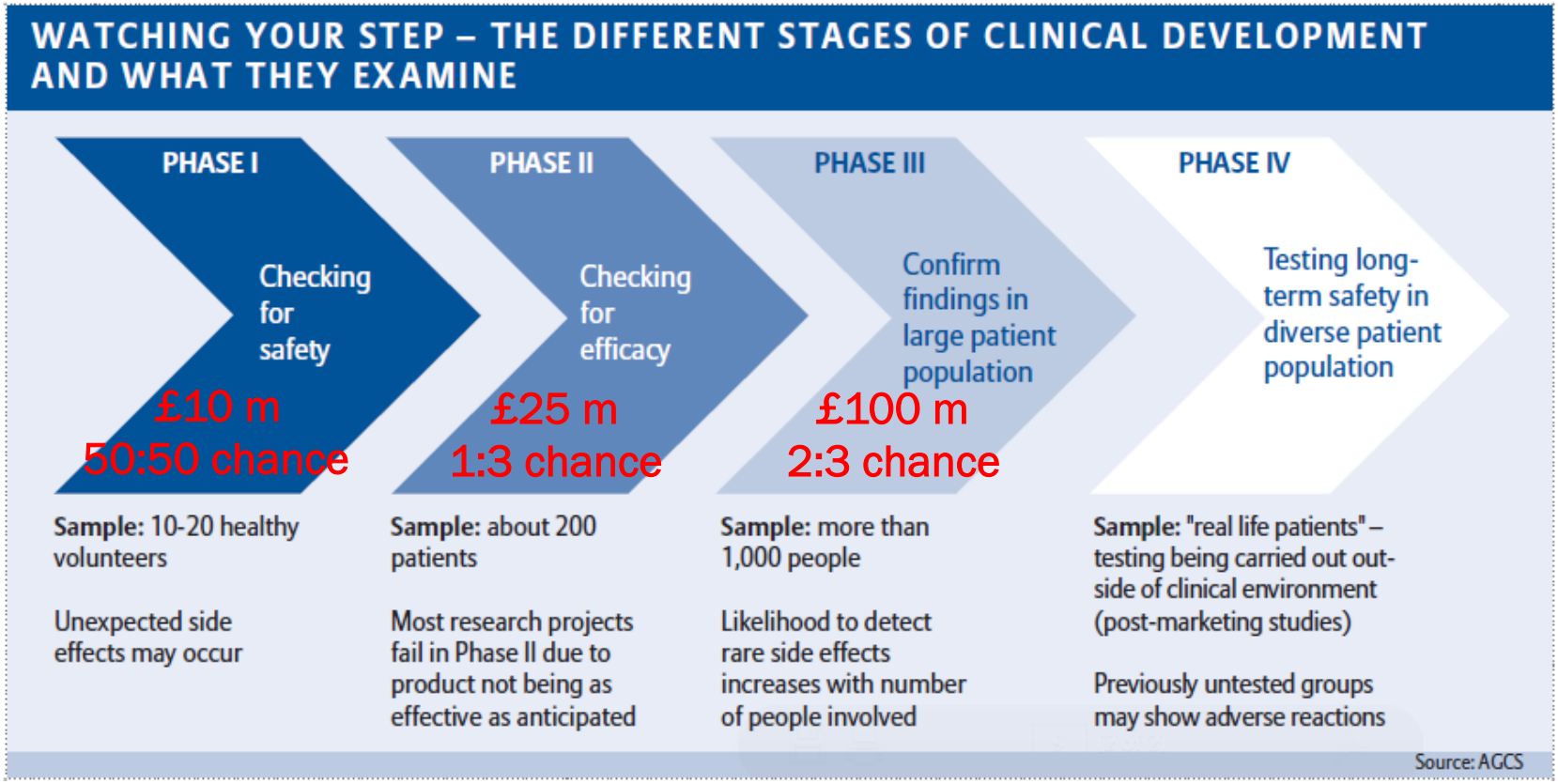


35 New Drug Approvals in 2011

$50 billion 2011 R&D expenditure

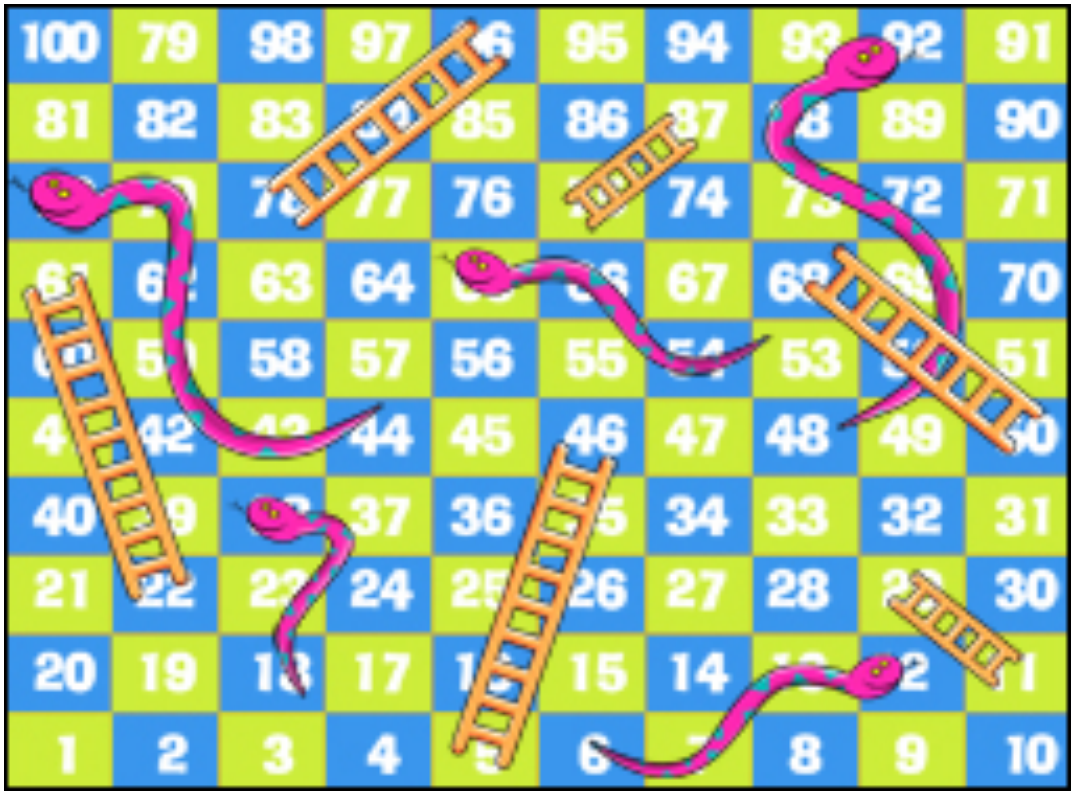
- 50/35 = $1.4 billion/drug approval

Clinical Trials for New Drugs

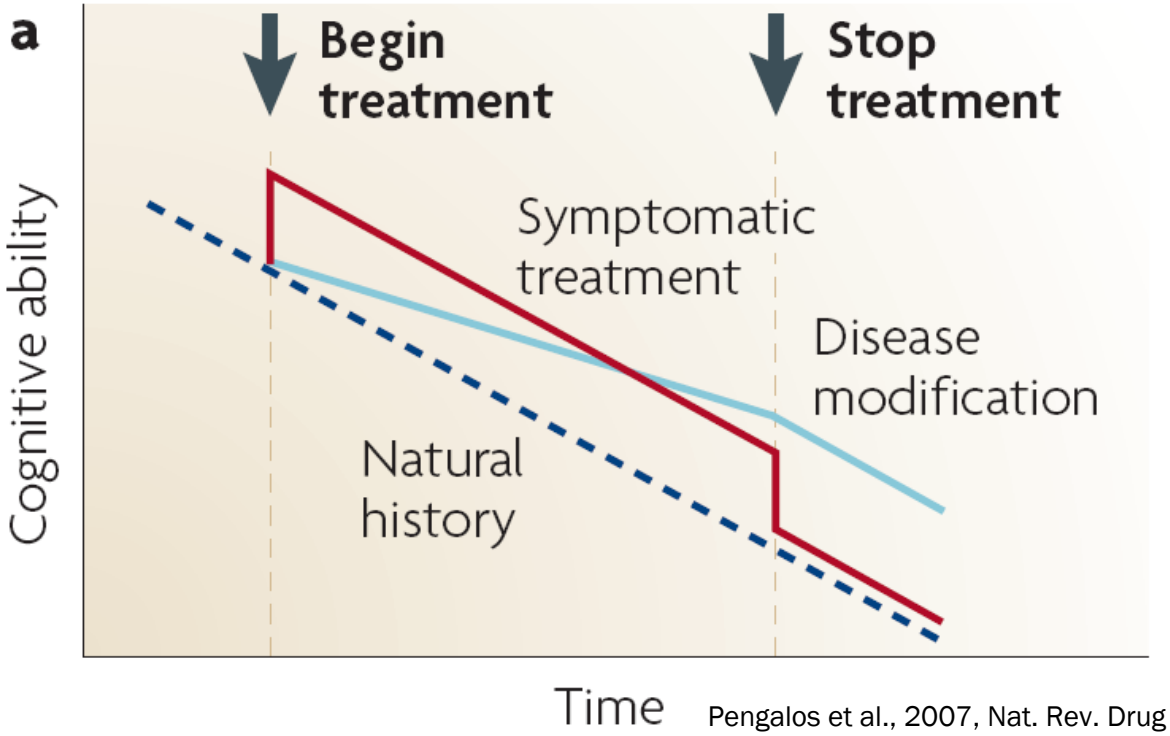


http://www.agcs.allianz.com/assets/PDFs/GRD/GRD%20individual%20articles/GRD_02_09_en%20Clinical%20Trials.pdf

The Drug Discovery Process in Pictures



Disease Modification vs Symptomatic Relief



Pengalos et al., 2007, Nat. Rev. Drug Discov., 6:521-532

- Disease modification needs understanding of pathology
  - Possible for neurodegenerative but not psychiatric disorders

General Strategies for Drug Discovery

- Serendipity
- Drug repositioning
- Take an existing drug and make it better
- Hypothesis-driven drug discovery based on an understanding of the disease process

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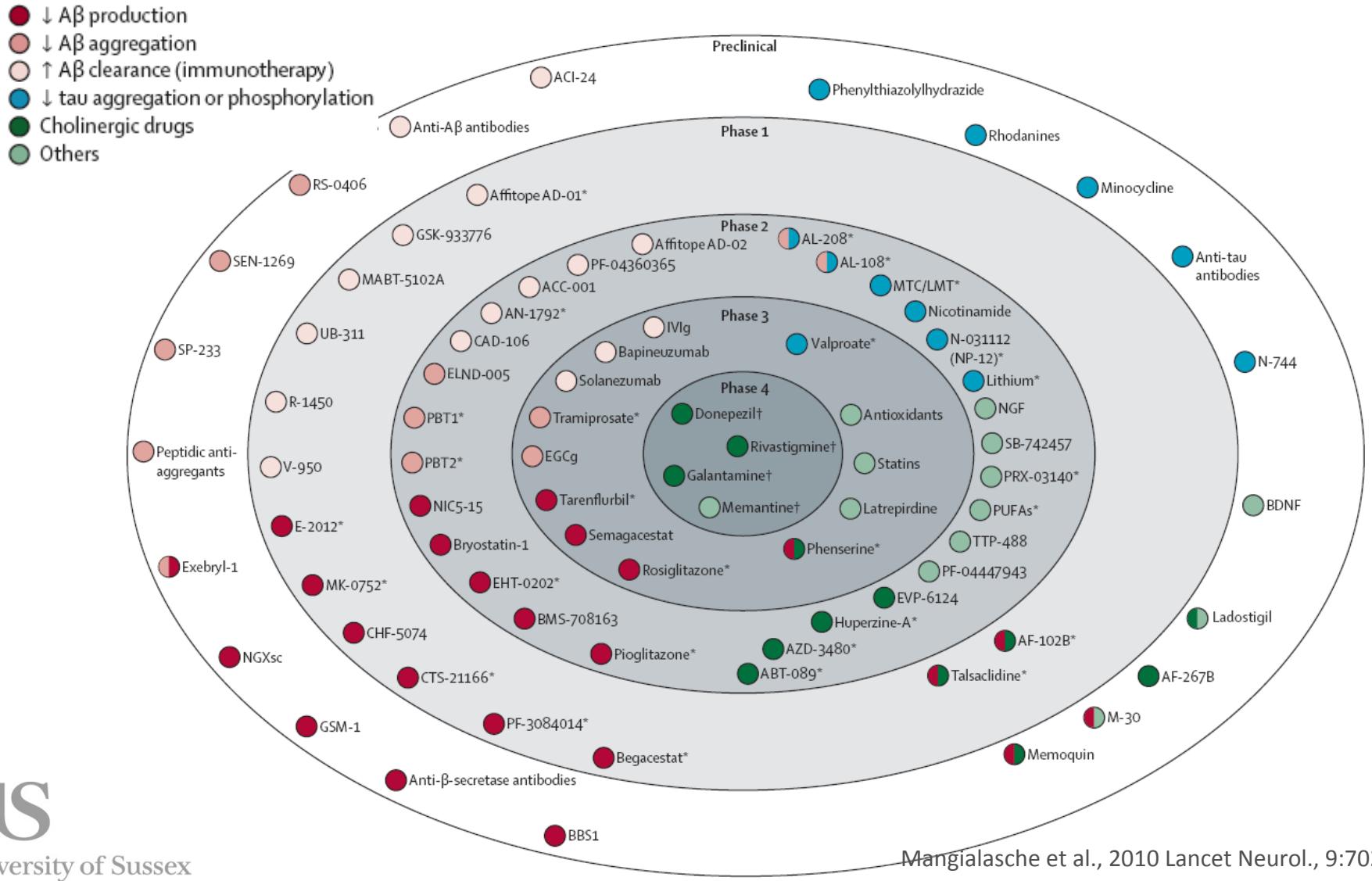
Overview of Alzheimer's Disease Drugs



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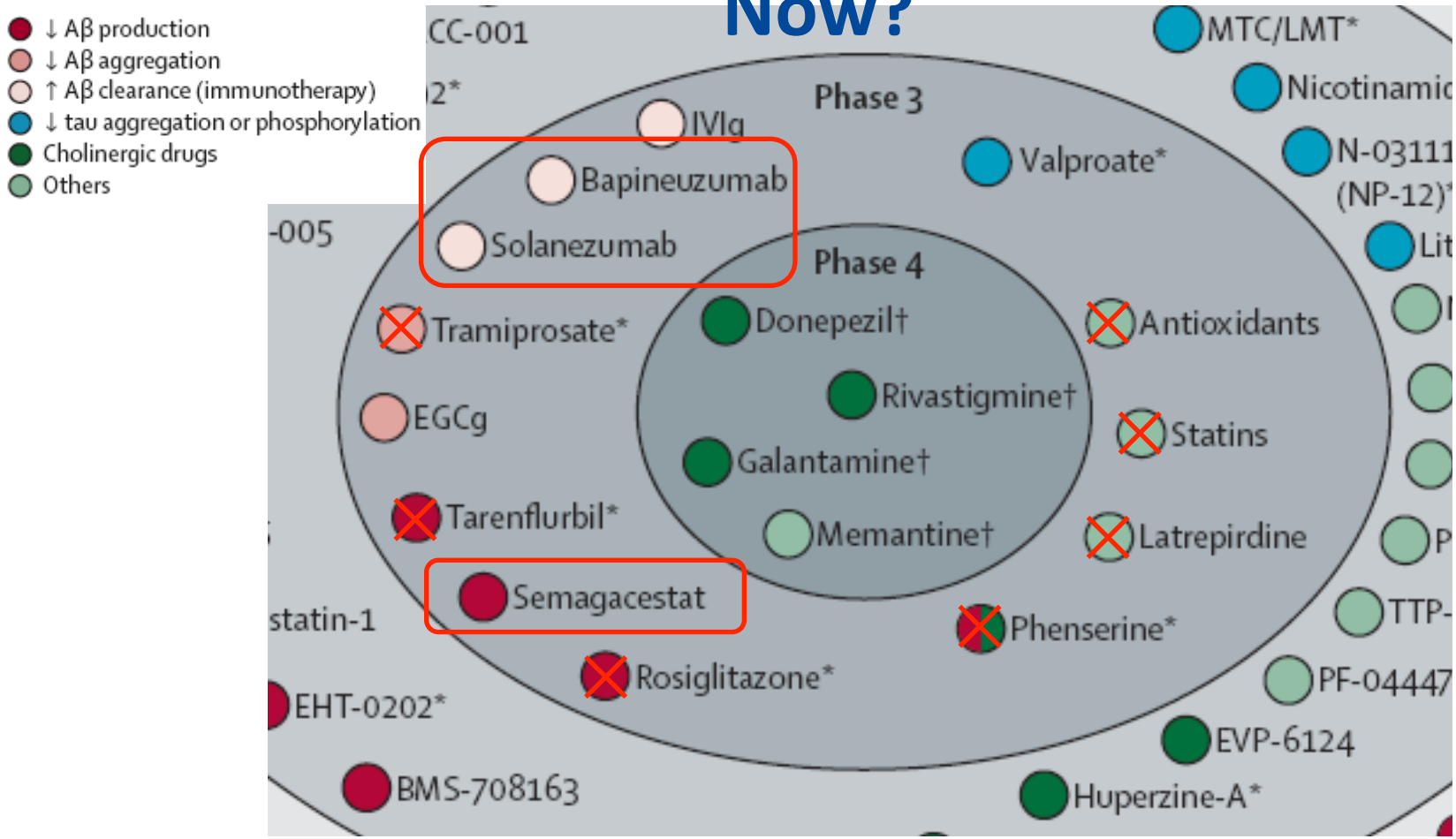
Mangialasche et al., 2010 Lancet Neurol., 9:702-716

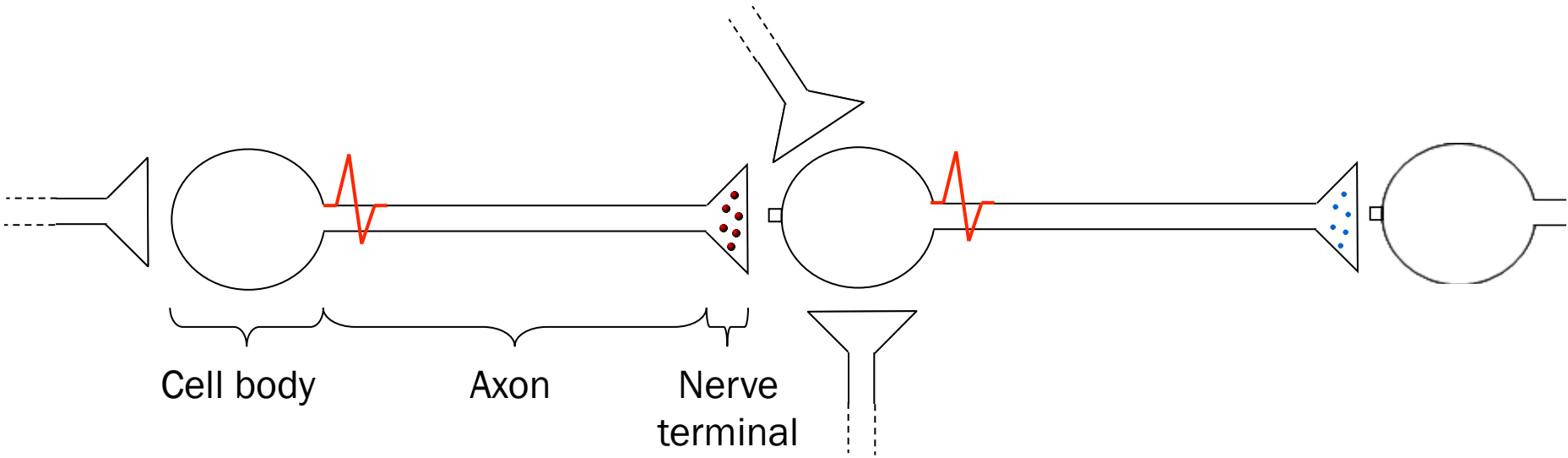
Alzheimer's Disease Drugs - Where Are We Now?



IVIg = intravenous immunoglobulins
EGCg = epigallocatechin-3-gallate (polyphenol from green tea)

Mangialasche et al., 2010
Lancet Neurol., 9:702-716

Treating the Symptoms – Understanding the Chemistry of the Brain



Many (>50) different chemicals involved

- Acetylcholine
- Dopamine
- Serotonin
- Noradrenaline
- Glutamate
- GABA
- Etc. etc

4 FDA-approved drugs for Alzheimer's Disease

Acetylcholinesterase (AChE) inhibitors

- Prevent the breakdown of acetylcholine
- 3 approved AChE inhibitors
  - Donepezil (Aricept) (Eisai/Pfizer) – FDA approval Dec 1996
  - Galantamine (Razadyne or Reminyl) (Forest/Janssen) – FDA approval Feb 2001
    - Originally isolated in the 1950s from snowdrops (*Galanthus* species)
  - Rivastigmine (Exelon) (Novartis) – FDA approval Apr 2000

N-Methyl-D-aspartate (NMDA) receptor antagonist

- Supposedly prevents glutamate-related neurotoxicity
  - Memantine (Namenda) (Merz/Forest & Lundbeck) – FDA approval Oct 2003

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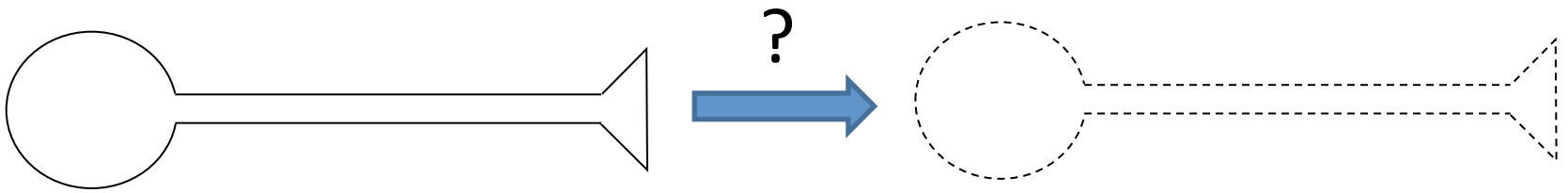
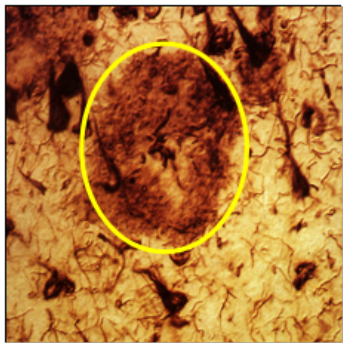
Disease Modification – Understanding How and Why Nerve Cells Dies



Potential clues to the disease process come from:

- Are there pathological changes in the brain and if so, what are they?
  - Plaques and tangles ✓
- Are there disease "clusters"?
  - Geography (environment), ✘ families (genetic) ✓
  - If yes, do we understand these clusters? ✓
- Are there "risk factors" associated with aging
  - Aging, ApoE ✓
  - If yes, do we understand these clusters? ✘

Modifying the Disease – Understanding What Goes Wrong in Alzheimer's Disease - 1



Vol. 120, No. 3, 1984
May 16, 1984
BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
Pages 885-890

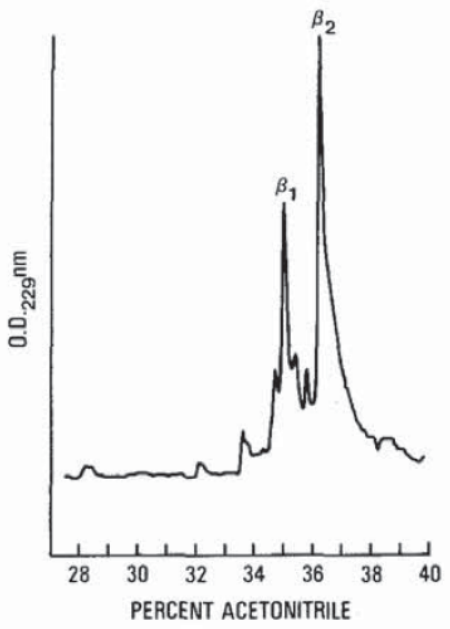
ALZHEIMER'S DISEASE: INITIAL REPORT OF THE PURIFICATION AND CHARACTERIZATION OF A NOVEL CEREBROVASCULAR AMYLOID PROTEIN

George G. GLENNER, M.D. and Caine W. WONG

University of California, San Diego (M-012), La Jolla, CA 92093

Received April 2, 1984

SUMMARY: A purified protein derived from the twisted β-pleated sheet fibrils in cerebrovascular amyloidosis associated with Alzheimer's disease has been isolated by Sephadex G-100 column chromatography with 5 M guanidine-HCl in 1 N acetic acid and by high performance liquid chromatography. Amino acid sequence analysis and a computer search reveals this protein to have no homology with any protein sequenced thus far. This protein may be derived from a unique serum precursor which may provide a diagnostic test for Alzheimer's disease and a means to understand its pathogenesis.



HPLC of cerebrovascular amyloid fibril protein β from a patient with Alzheimer's disease, previously isolated on Sephadex G-100, reveals two major protein peaks (β_1 and β_2), each of similar amino acid composition and identical amino-terminal amino acid sequence (Table 2).

Table 2. Sequence of Cerebrovascular Amyloid Protein

NH_2-Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Gln-Val-
His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val---COOH

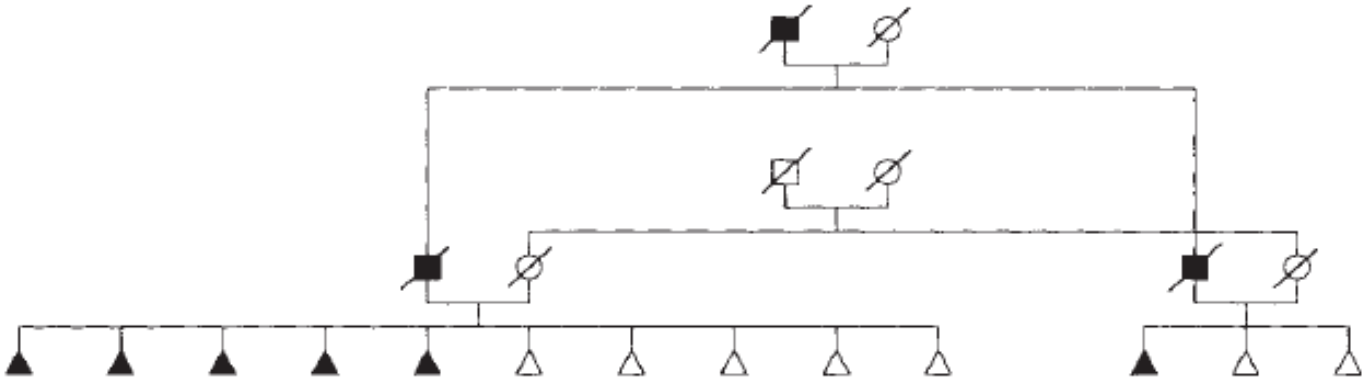
- Senile plaques contain a 40-42 amino acid protein called amyloid

Modifying the Disease – Understanding What Goes Wrong in Alzheimer's Disease - 2

Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease

Alison Goate*, Marie-Christine Chartier-Harlin*, Mike Mullan*, Jeremy Brown*, Fiona Crawford*, Liana Fidani*, Luis Giuffra†, Andrew Haynes‡, Nick Irving*, Louise James‡, Rebecca Mant‖, Phillippa Newton*, Karen Rooke*, Penelope Roques*, Chris Talbot*, Margaret Pericak-Vance§, Allen Roses§, Robert Williamson*, Martin Rossor*, Mike Owen‖ & John Hardy*¶

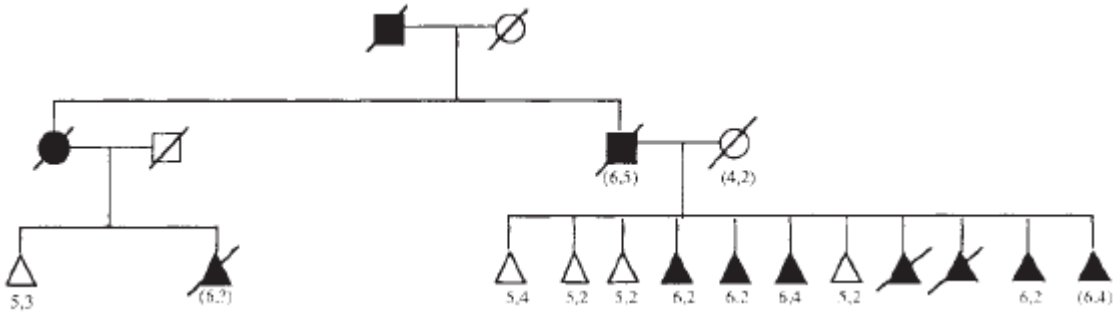
* Alzheimer's Disease Research Group, Departments of Biochemistry and Neurology, St Mary's Hospital Medical School, London W2 1PG, UK
† Department of Human Genetics, Yale University Medical School, 333 Cedar Street, New Haven, Connecticut 06150, USA
§ Duke University Medical Center, Durham, North Carolina NC 27710, USA
‖ Departments of Psychological Medicine and Medical Genetics, University of Wales College of Medicine, Cardiff CF4 4XN, UK



Early-onset Alzheimer's disease caused by mutations at codon 717 of the β-amyloid precursor protein gene

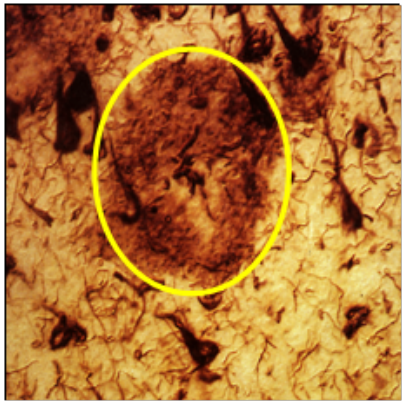
Marie-Christine Chartier-Harlin, Fiona Crawford, Henry Houlden, Andrew Warren*, David Hughes, Liana Fidani, Alison Goate, Martin Rossor, Penelope Roques, John Hardy & Mike Mullan†

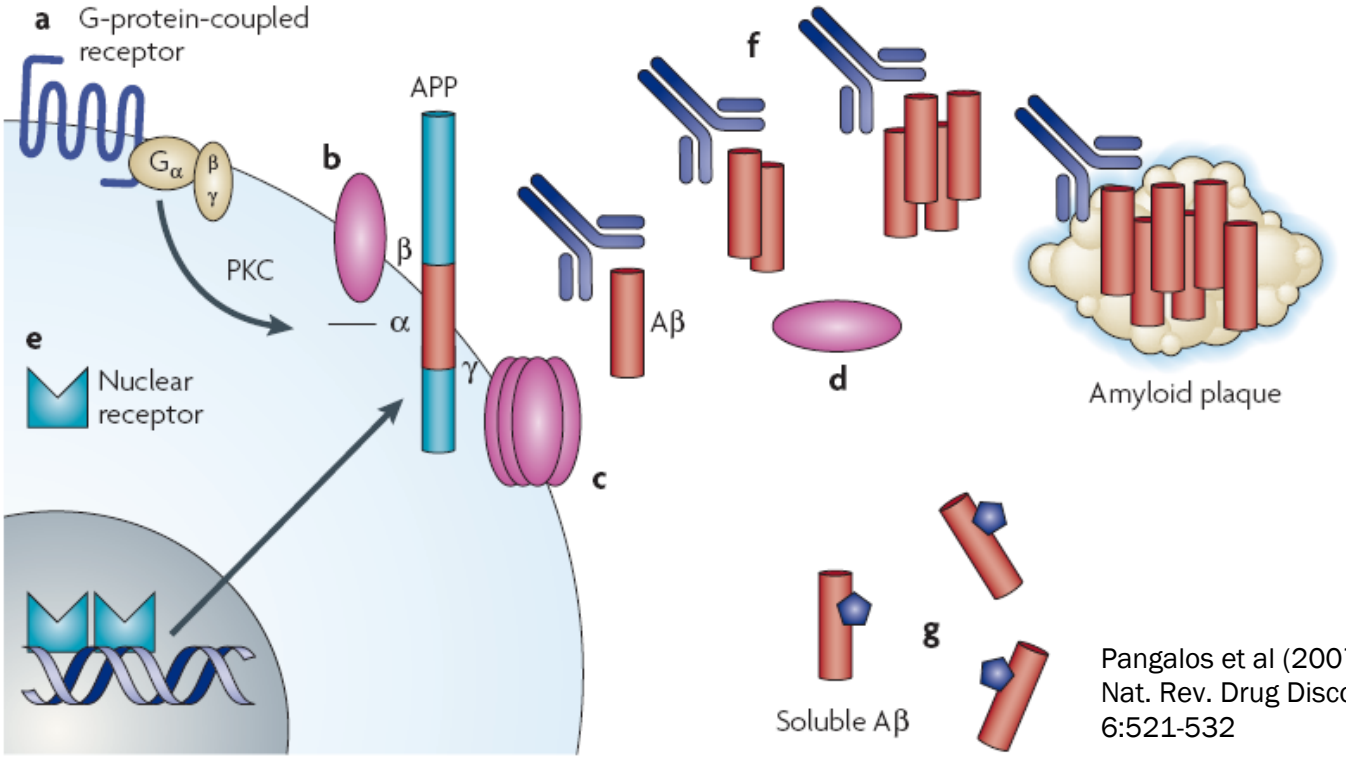
Alzheimer's Disease Research Group, Departments of Biochemistry and Neurology, St Mary's Hospital Medical School, Imperial College, London W2 1PG, UK
* Departments of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA
† To whom correspondence should be addressed



- Familial AD is associated with mutations in amyloid

Placing Your Bets – Amyloid in AD





Pangalos et al (2007) Nat. Rev. Drug Discov., 6:521-532

Reduce Aβ formation

a GPCR modulation of APP processing

b BACE1 inhibition

c γ-secretase

GS inhibitor, GS modulator

Increase Aβ clearance

d Activate Aβ degrading enzymes

Neprilysin, insulin-degrading enzyme

e Modulation of gene transcription

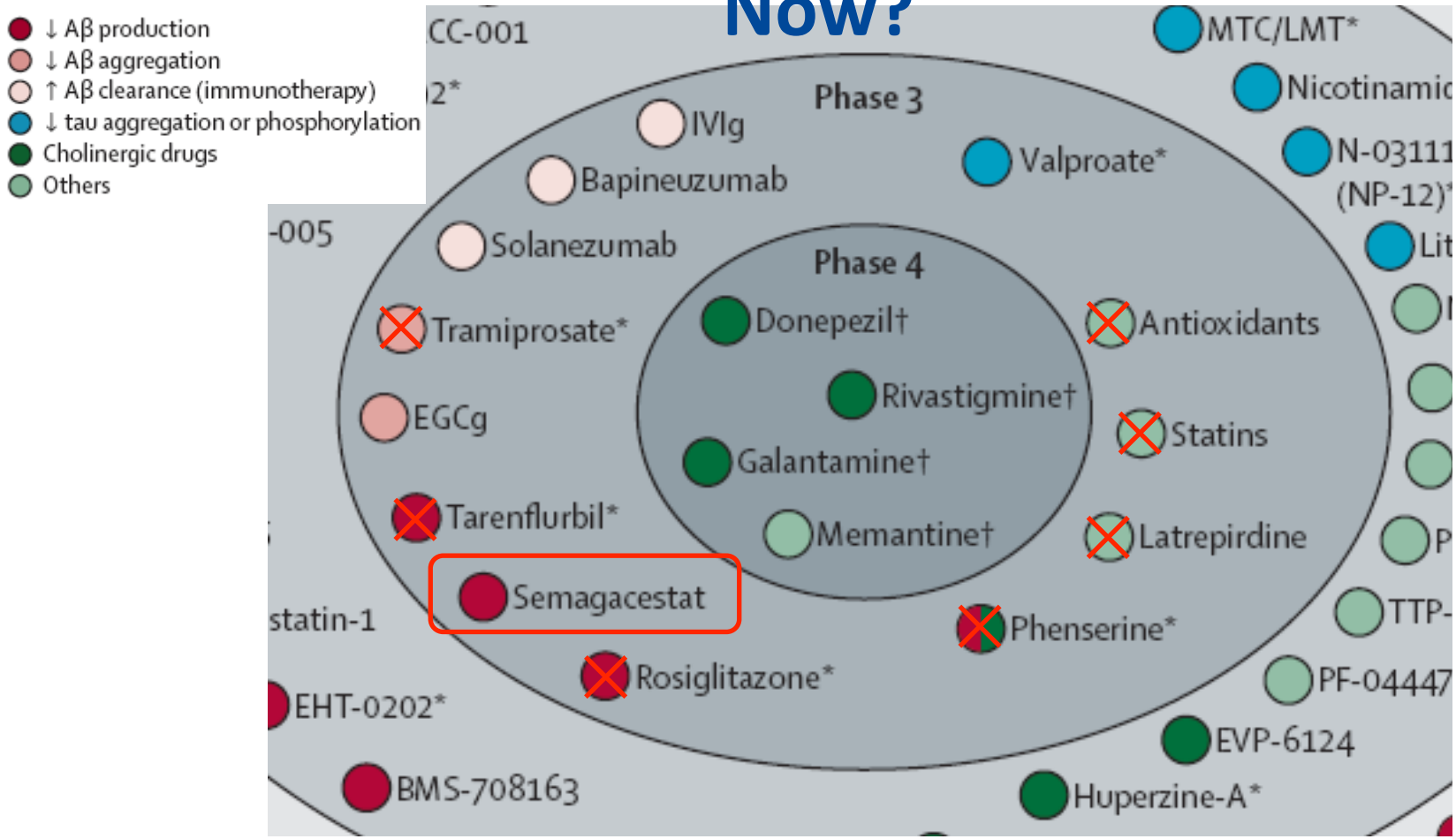
f Antibodies

Bapineuzumab, Solanezumab

Other approaches

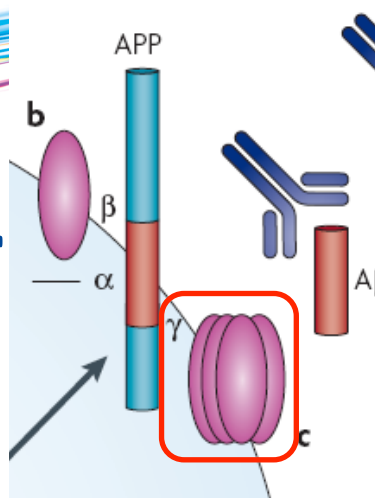
g Aggregation inhibitors

Alzheimer's Disease Drugs - Where Are We Now?



Mangialasche et al., 2010 Lancet Neurol., 9:702-716

Semagacestat – γ-Secretase Inhibitor



- γ-secretase inhibition should reduce amyloid
  - deterioration in cognition should slow down

Lilly Halts Development of Semagacestat for Alzheimer's Disease Based on Preliminary Results of Phase III Clinical Trials

TOOLS Email Print

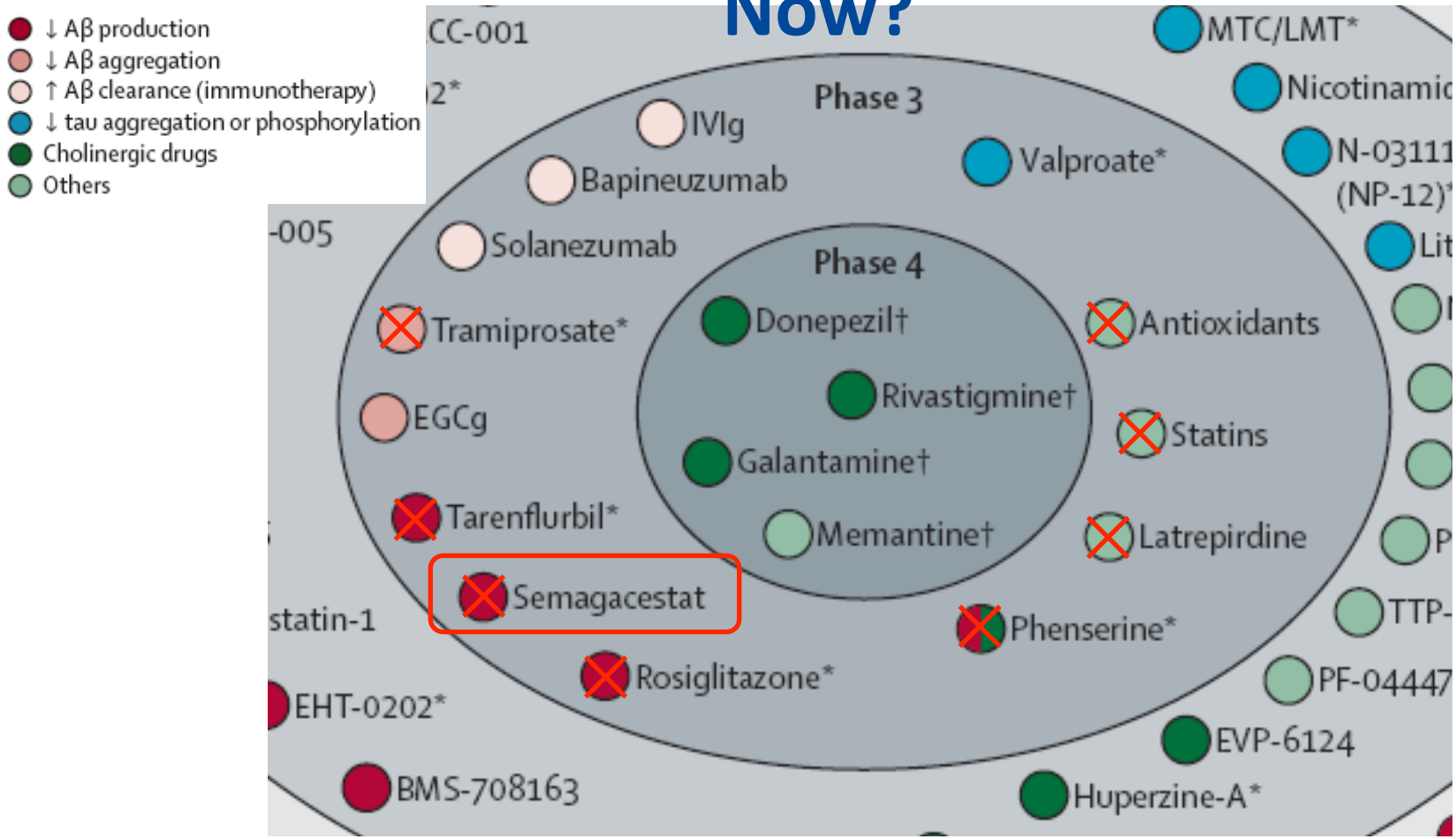
Posted August 17, 2010

Decision does not affect other Lilly Alzheimer's compounds in development

INDIANAPOLIS, Aug. 17 /PRNewswire-FirstCall/ -- Eli Lilly and Company (NYSE: LLY) will halt development of semagacestat, a gamma secretase inhibitor being studied as a potential treatment for Alzheimer's disease, because preliminary results from two ongoing long-term Phase III studies showed it did not slow disease progression and was associated with worsening of clinical measures of cognition and the ability to perform activities of daily living.

- Semagacestat (LY450139) studies stopped following interim analysis
  - Cognition became worse and skin cancer incidence increased
  - Not clear why Semagacestat had these effects

Alzheimer's Disease Drugs - Where Are We Now?



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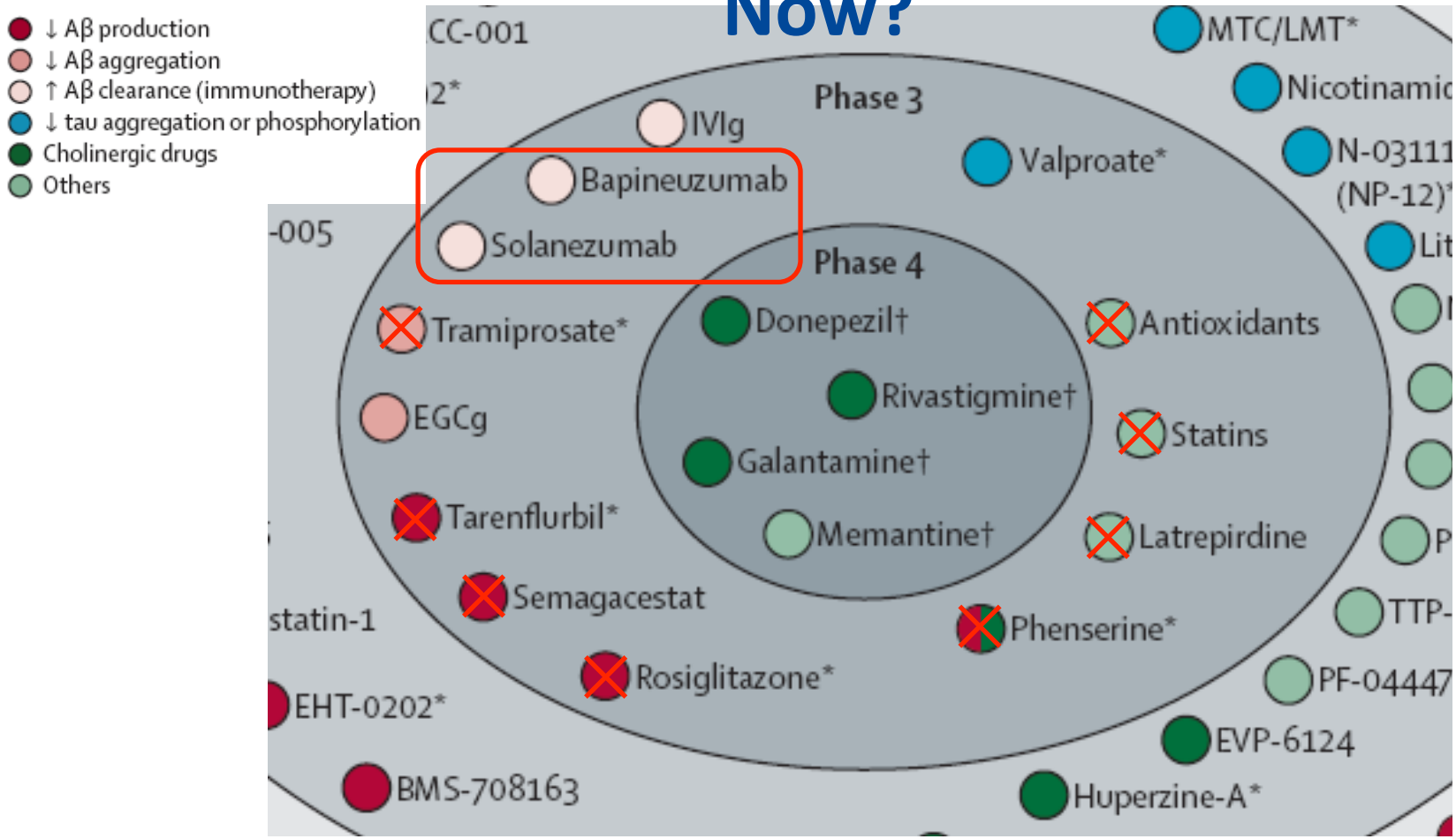
Alzheimer's Disease Drugs - Where Are We Now?



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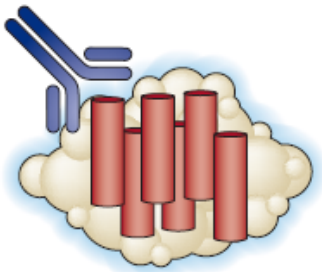
Bapineuzumab – Phase 3 Failure



Amyloid plaque

Topics: Clinical Trials | Pipeline

UPDATED: Pfizer, J&J kill PhIII program for key Alzheimer's drug

August 6, 2012 | By Ryan McBride

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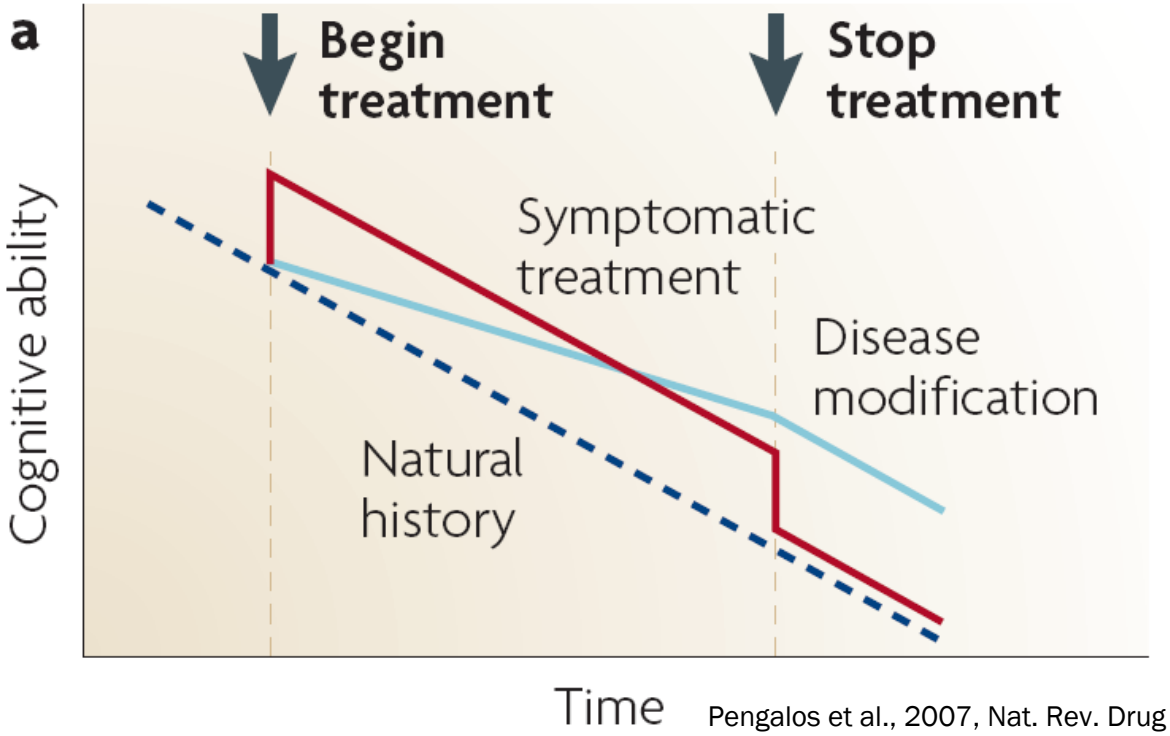
Pfizer ($PFE) and Johnson & Johnson ($JNJ) have nixed development of one of the most closely watched drugs in their pipelines, bapineuzumab, after two Phase III clinical trials for the experimental Alzheimer's therapy ended in failure. The decision comes as no surprise as the program was given slim odds of success. But many are following bapi, one of the most advanced drugs for combating beta amyloid that builds up in the brain and is a suspected cause of the common memory-stealing disease.

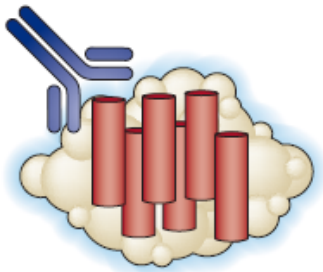
Trouble for the program surfaced last month after bapi fell short in improving a key measure of cognition compared with placebo in a Phase III trial involving Alzheimer's patients who are ApoE4 gene carriers. On Monday, the companies reported that the second of four late-stage studies of the drug--this one involving patients with ApoE4 non-carriers--failed as well. And they have decided to end all trials for the drug from Irish drugmaking partner Elan ($ELN), ceasing development of their blockbuster hopeful.

Disease Modification vs Symptomatic Relief

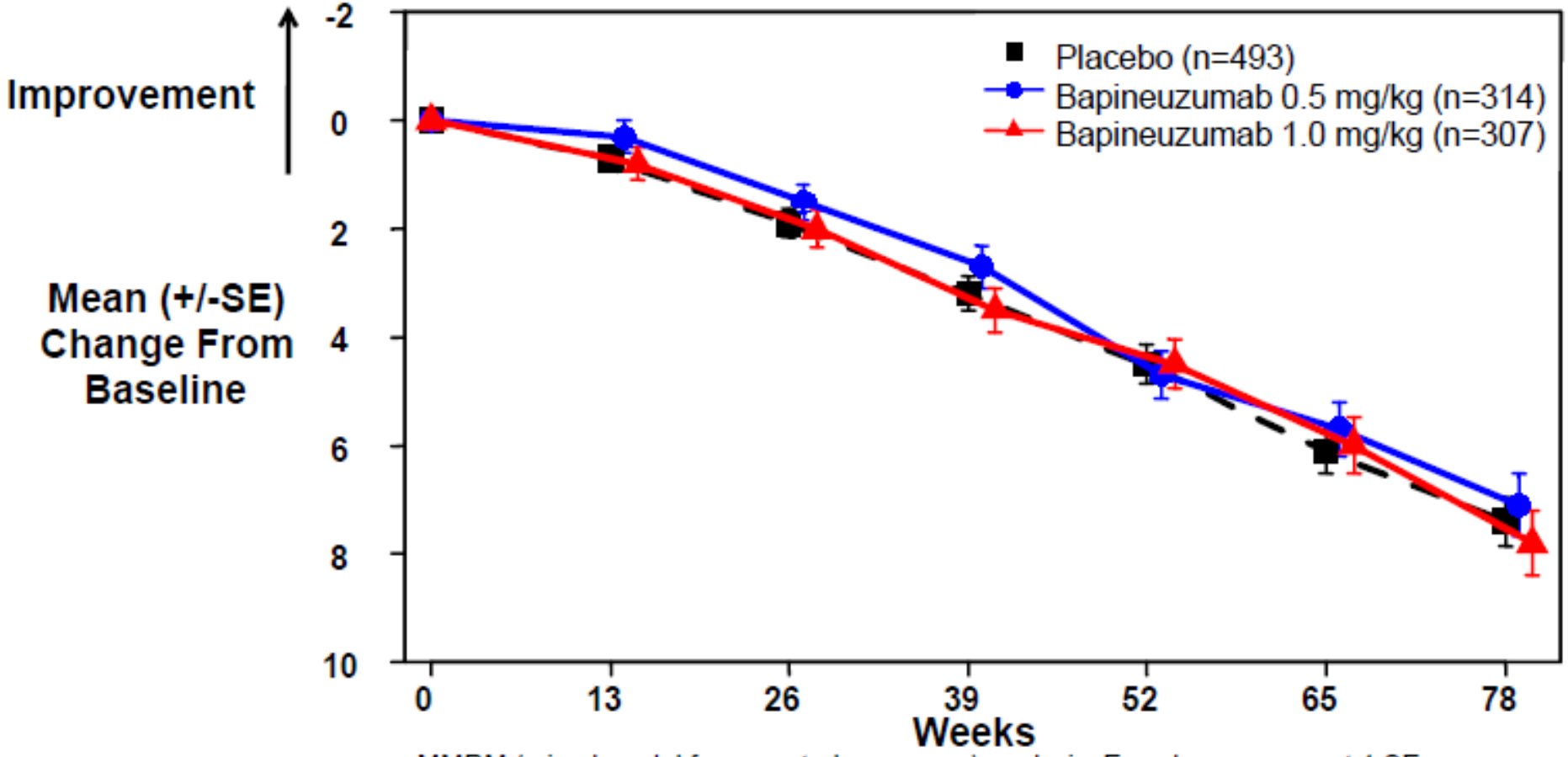


Pengalos et al., 2007, Nat. Rev. Drug Discov., 6:521-532

Bapineuzumab – Phase 3 ADAS-Cog

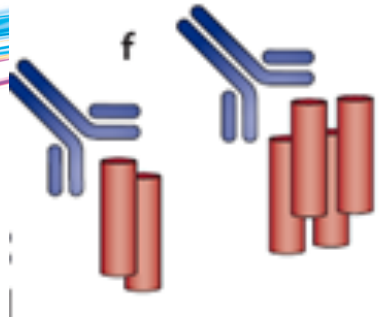


Amyloid plaque



MMRM (mixed model for repeated measures) analysis. Error bars represent 1 SE.

Solanezumab - Phase 3 Failure



Topics: Clinical Trials

Lilly's Alzheimer's drug solanezumab flunks out, but CEO sees promise

August 24, 2012 | By John Carroll

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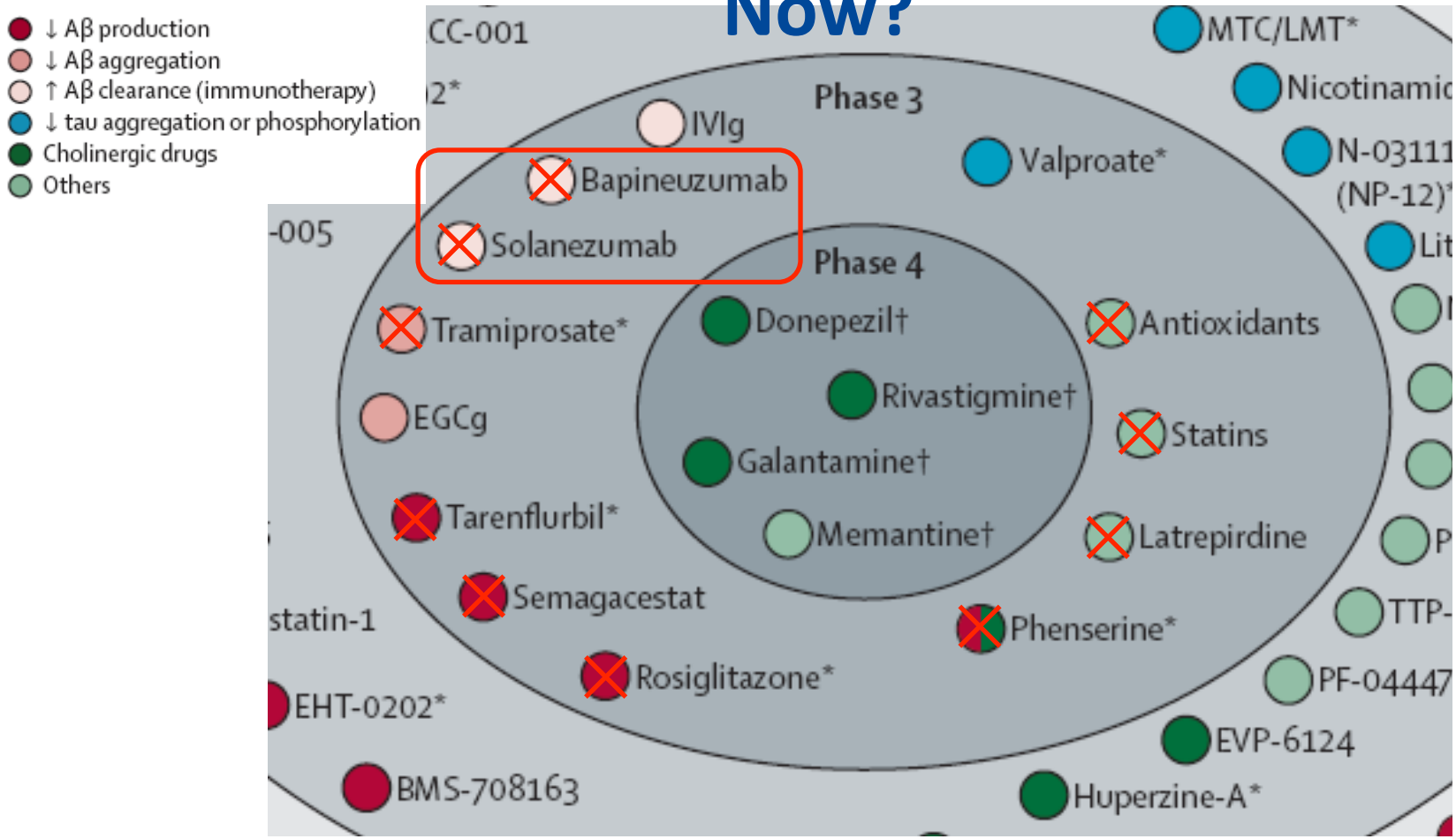
TOOLS

After enduring months of criticism about its late-stage effort to determine the efficacy of the last big Phase III hope for Alzheimer's, Eli Lilly ($LLY) this morning announced that solanezumab flunked both primary endpoints. The failure, widely forecast by a long lineup of analysts, will raise more doubts about the theory that cutting levels of toxic amyloid beta in patients with mild to moderate Alzheimer's can help patients with the disease.

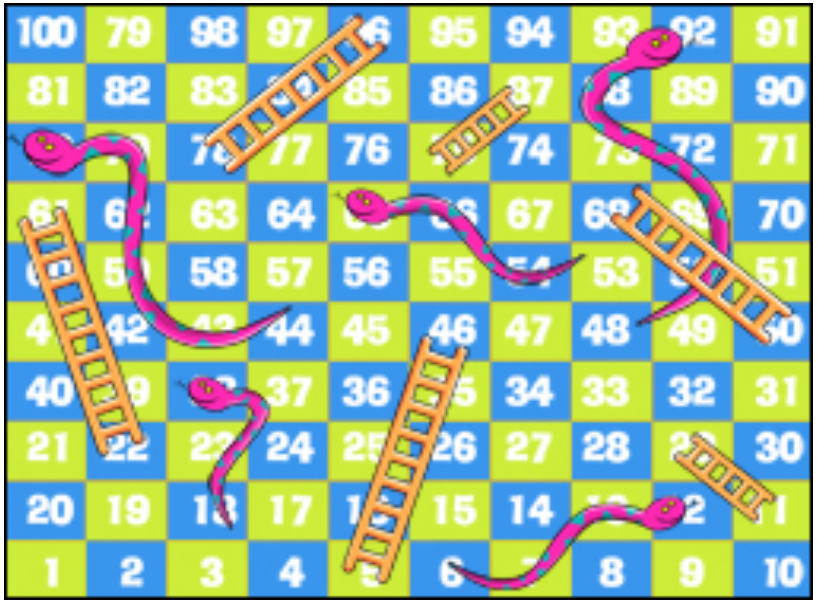
Lilly, though, isn't giving up on the drug, its second major try at treating Alzheimer's. CEO John Lechleiter, who has bet his job that the company's R&D division can develop a new generation of therapies, noted that a secondary analysis of pooled data "showed statistically significant slowing of cognitive decline in the overall study population of patients with mild-to-moderate Alzheimer's disease. In addition, pre-specified secondary subgroup analyses of pooled data across both studies showed a statistically significant slowing of cognitive decline in patients with mild Alzheimer's disease, but not in patients with moderate Alzheimer's disease."

Alzheimer's Disease Drugs - Where Are We Now?



Mangialasche et al., 2010 Lancet Neurol., 9:702-716

Pictorial Summary of Recent Clinical Data



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INDEPENDENT

Drug giants give up on Alzheimer's cure

Research too difficult and costly, say pharmaceutical companies

By **JEREMY LAURANCE**
Health Editor

The world's leading pharmaceutical companies are downgrading the search for new treatments for Alzheimer's disease after the failure of a series of high-profile drugs trials.

The human and financial costs of the disease are growing rapidly as the population ages, but the prospects of treatments to halt it, or slow its progress, are receding as at least five trials in the past five years have delivered disappointing results.

This year, a trial of Dimebon, backed by Pfizer, the US pharmaceutical giant, and reported in January, failed to show any benefit, instead costing the company $750m in lost investment.

In July, bapineuzumab, developed by Irish drug-maker Elan in association with Pfizer and the US multinational Johnson & Johnson, also failed to show an impact on symptoms.

In August, another US group, Eli Lilly, reported the failure of solanezumab, its second Alzheimer's drug to disappoint in two years. In 2010, a trial of semagacestat not only failed to slow the disease but worsened symptoms.

The setbacks have damaged confidence among drug makers in the field of neuroscience – brain research – which was already shaky.

Pharmaceutical manufacturers worldwide are under pressure and have been cutting back in the recession, but neuroscience has been disproportionately hit, with AstraZeneca, Pfizer, Merck, Sanofi, Novartis and GlaxoSmithKline all downsizing

Continued on **PAGE 6**

Capita to be paid bounty for catching illegal immigrants

By **NIGEL MORRIS**
Deputy Political Editor

Ministers were accused last night of placing a "bounty" on illegal immigrants' heads after the UK Border Agency announced that a private company will be brought in to track down more than 170,000 people still in the country after their visas expired.

Capita will be paid up to £30m on a payment-by-results basis.

Full report, **PAGE 15**

The Independent, 19 September, 2012

Outline of Presentation

- Introduction to Alzheimer's Disease
- The Drug Discovery Process
- Current Drugs for Alzheimer's Disease
- Amyloid-related drugs for Alzheimer's Disease
  - Segamacestat
  - Bapineuzumab, Solanezumab
- What happens next?

Drugs for Testing Amyloid Hypothesis

2 interpretations of the data

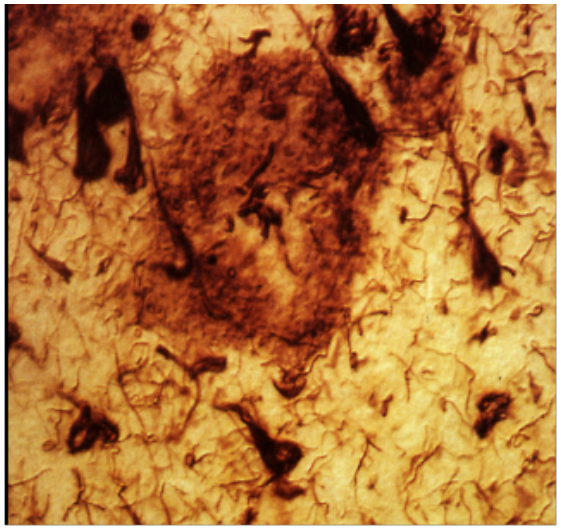
- Drugs not good enough
  - Use drugs that are better than bapineuzumab, solanezumab and segamacetat
- Drugs are good enough but we need to use them much earlier
  - Evaluate drug in prevention trials

Drug Treatment – Timing is Everything

Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade

Clifford R Jack Jr, David S Knopman, William J Jagust, Leslie M Shaw, Paul S Aisen, Michael W Weiner, Ronald C Petersen, John Q Trojanowski

Lancet Neurol 2010; 9: 119–28



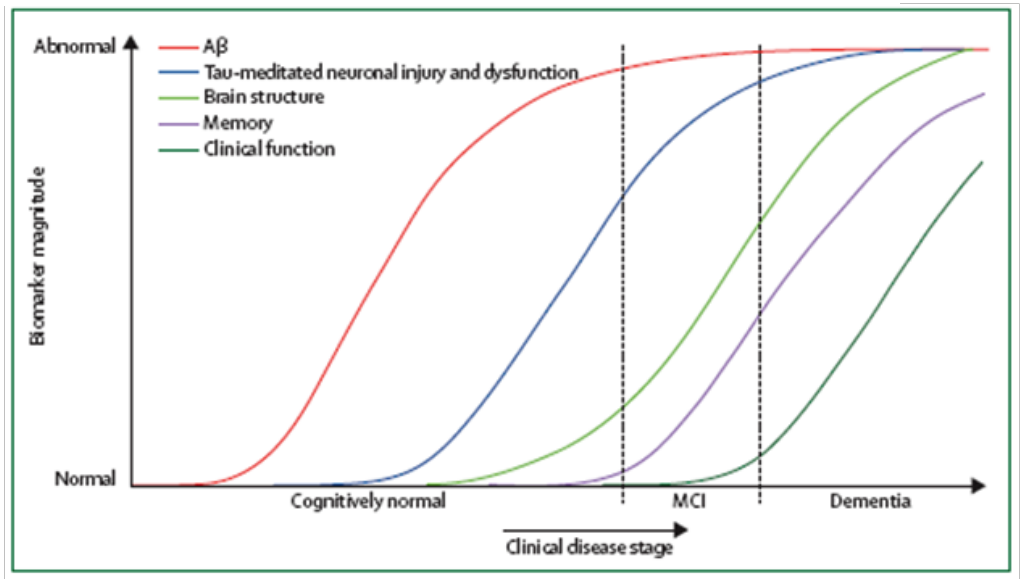


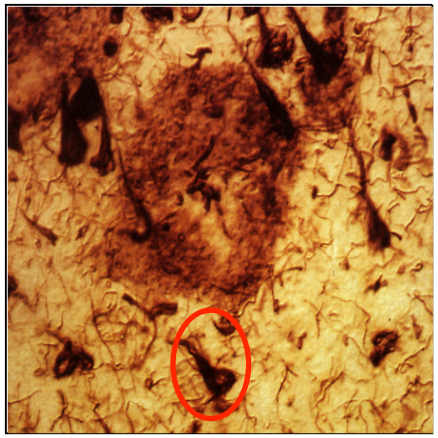
Figure 2: Dynamic biomarkers of the Alzheimer's pathological cascade
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.

- ADNI provides an in vivo view on disease progression
  - Amyloid pathology might be complete by the time symptoms occur

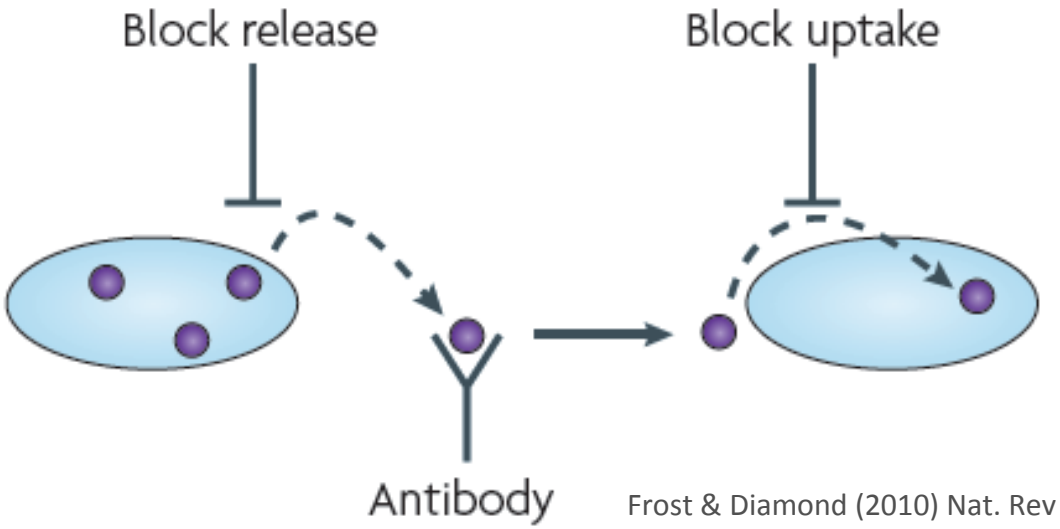
Alzheimer's Disease Prevention Trial

- Can drug treatment prevent AD occurring in a family with APP mutation?
  - Columbian family with γ-secretase presenilin-1 E280A mutation
  - 3-arm, 5-year study
    - 100 E280A family members receive placebo
    - 100 E280A family members receive Genentech Crenezumab antibody
    - 100 non-E280A family members receive placebo
  - philanthropic (Banner Institute), public (NIH) and private (Genentech) funding of roughly $15:$16:$65 million

Alzheimer's Disease Neurofibrillary Tangles



- Neurofibrillary tangles (NFTs) contain paired helical filaments
  - hyperphosphorylated tau (2-3 phosphates → 8-9 phosphates)

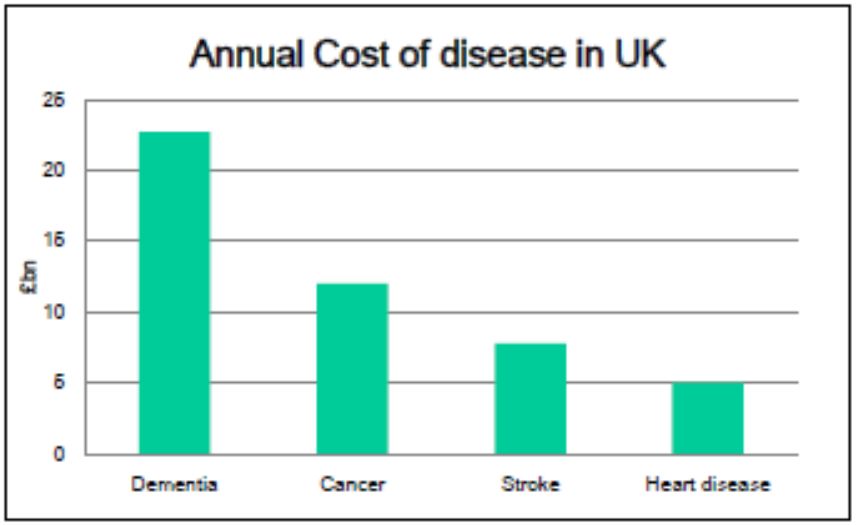


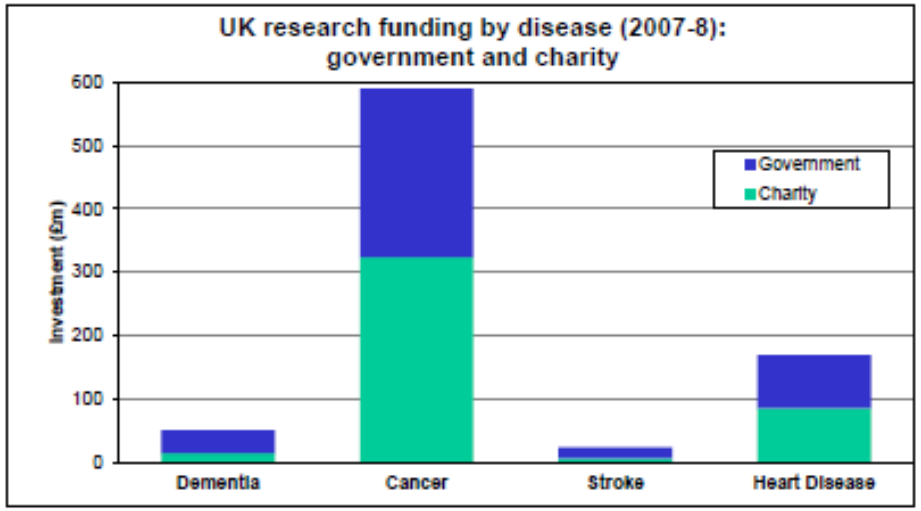
Frost & Diamond (2010) Nat. Rev Neurosci., 11:155-159

Summary

- The last 30 years have seen huge advances in our understanding of Alzheimer's Disease
- The amyloid hypothesis has dominated recent drug discovery efforts
  - Several high-profile failures
  - Each failure is a lesson learned
- Our understanding of Alzheimer's disease has advanced despite rather than because of research funding

Alzheimer's Disease Costs – 2007-8 Figures





Slide courtesy of Eric Karran, Scientific Director, Alzheimer's Research, UK