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A leader in AD Drug Development

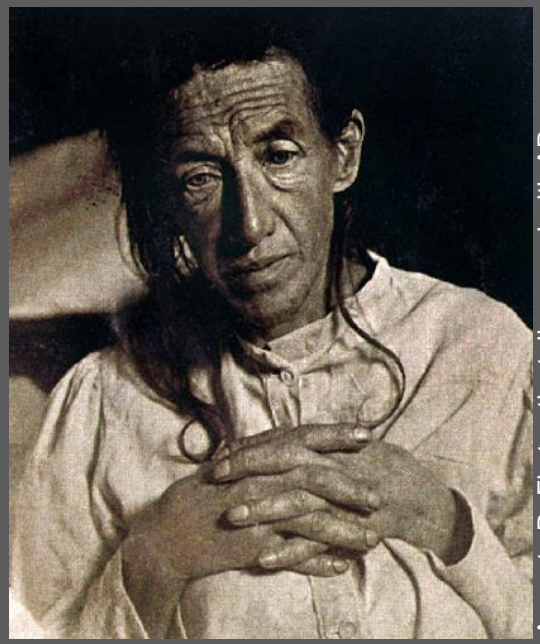
The Brain Forum 21st Century Challenge: Neurodegeneration

Prof. Andrea Pfeifer

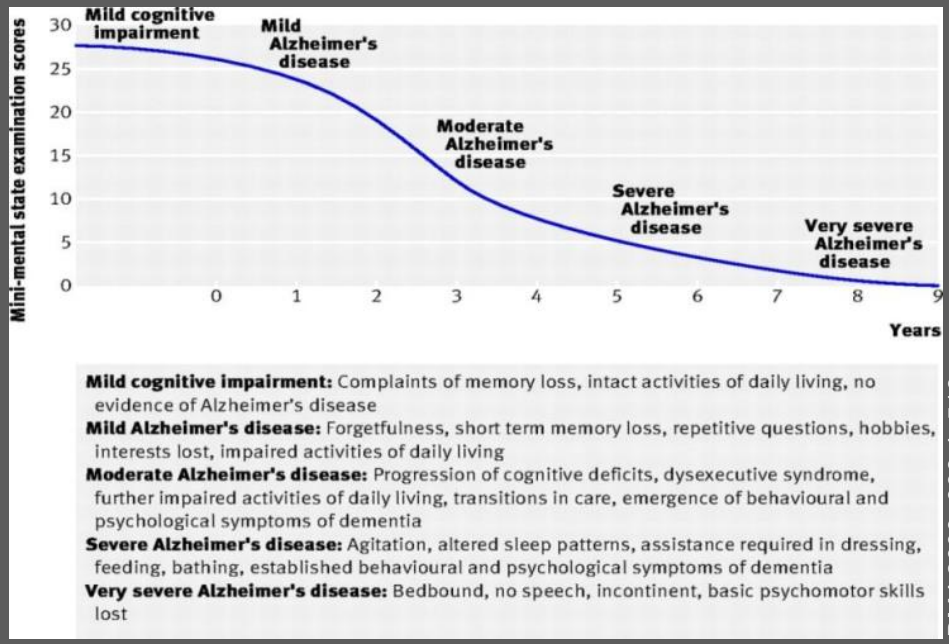
Lausanne - April 1st, 2015

Alzheimer´s disease
Most common neurodegenerative disease

- Devastating, irreversible neurodegenerative disease
- Terrible human burden for patients and families
  - Progressive destruction of patient's memory and senses
  - Alteration and destruction of people's personality
  - Late stage patients need nursing care 24h per day
- Alzheimer accounts for approx. 70% of all forms of dementia (WHO)



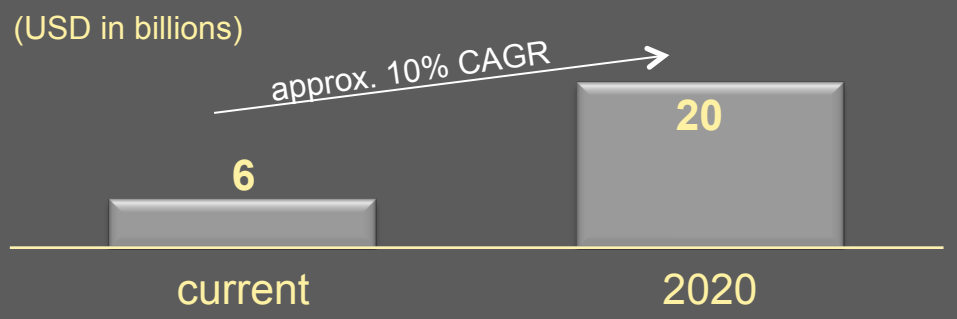
Auguste D. First patient diagnosed with AD



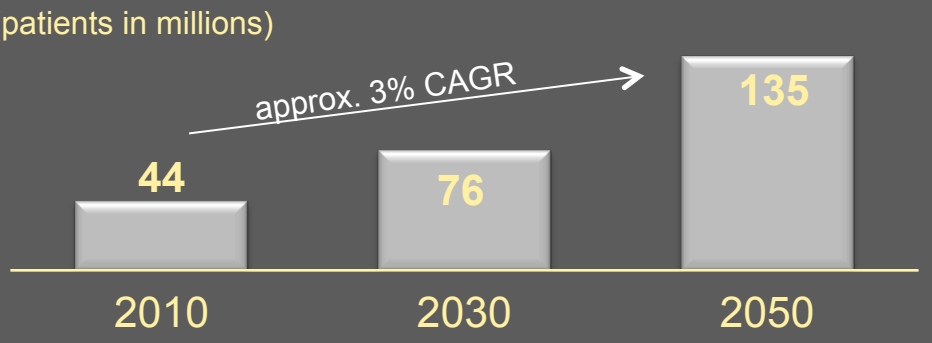
BMJ 2009, 338, b 518

Alzheimer's disease
Most significant Health Crisis of 21st Century

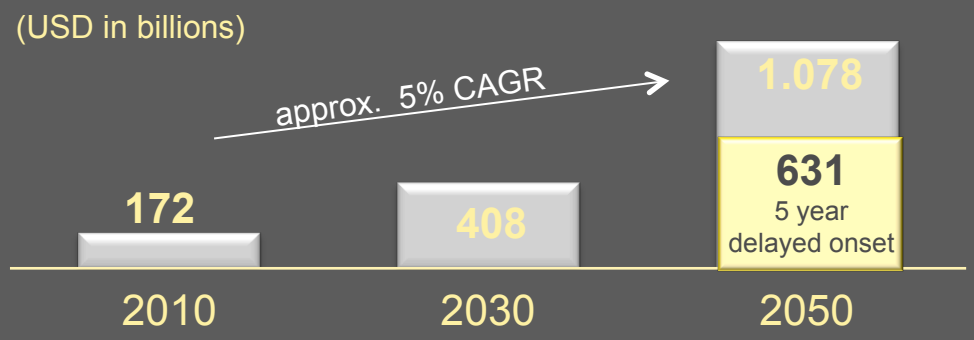
Worldwide therapeutic value



Worldwide patient population



US prevention and treatment costs



But no drug approval since more than 10 years!

Source: The World Alzheimers Report, 2013 Alzheimer's Disease International; BBC Research

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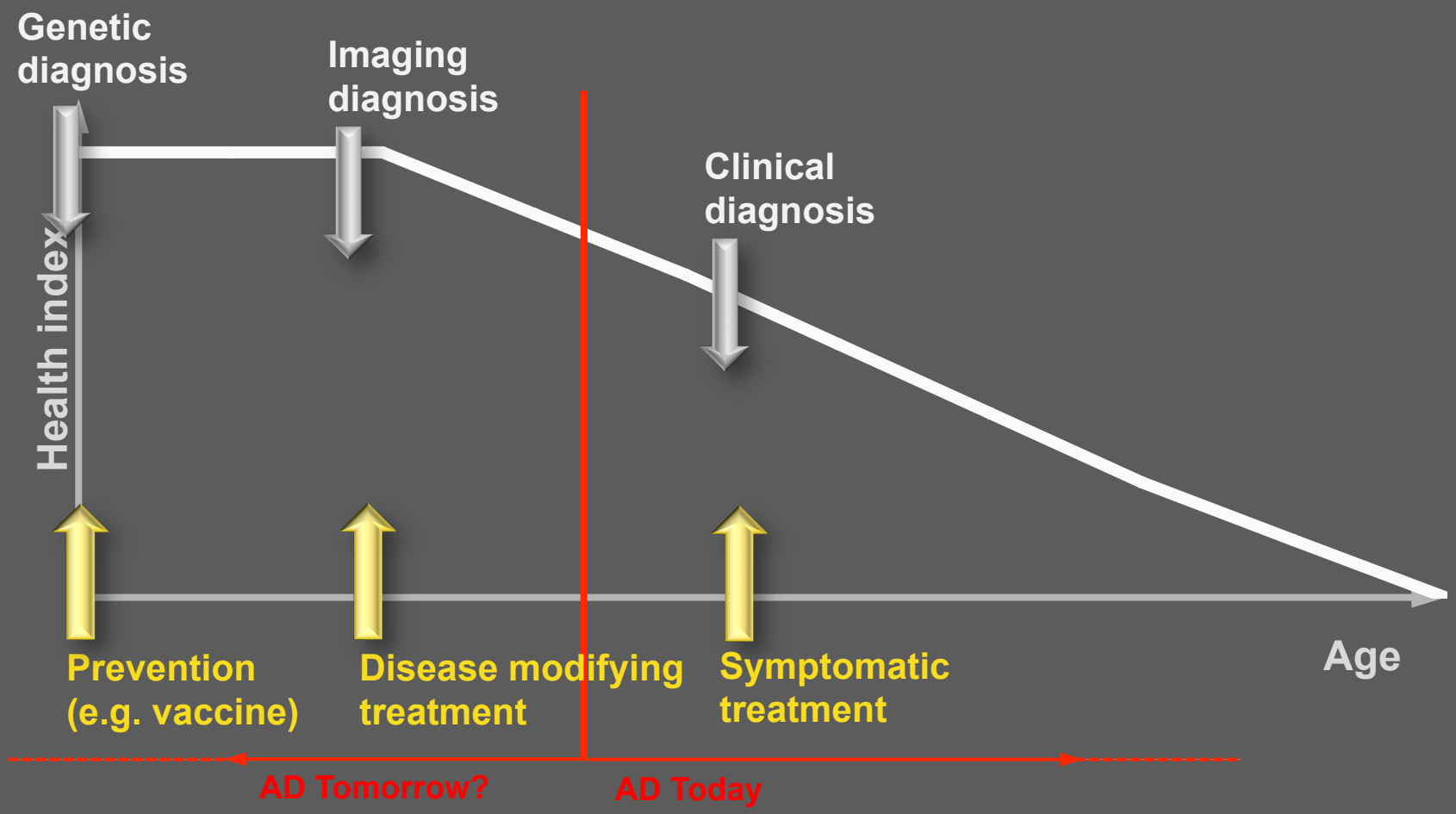
Alzheimer's disease - a large and growing market for efficient therapies and early diagnostics



Early diagnosis translates into earlier treatment and better outcome

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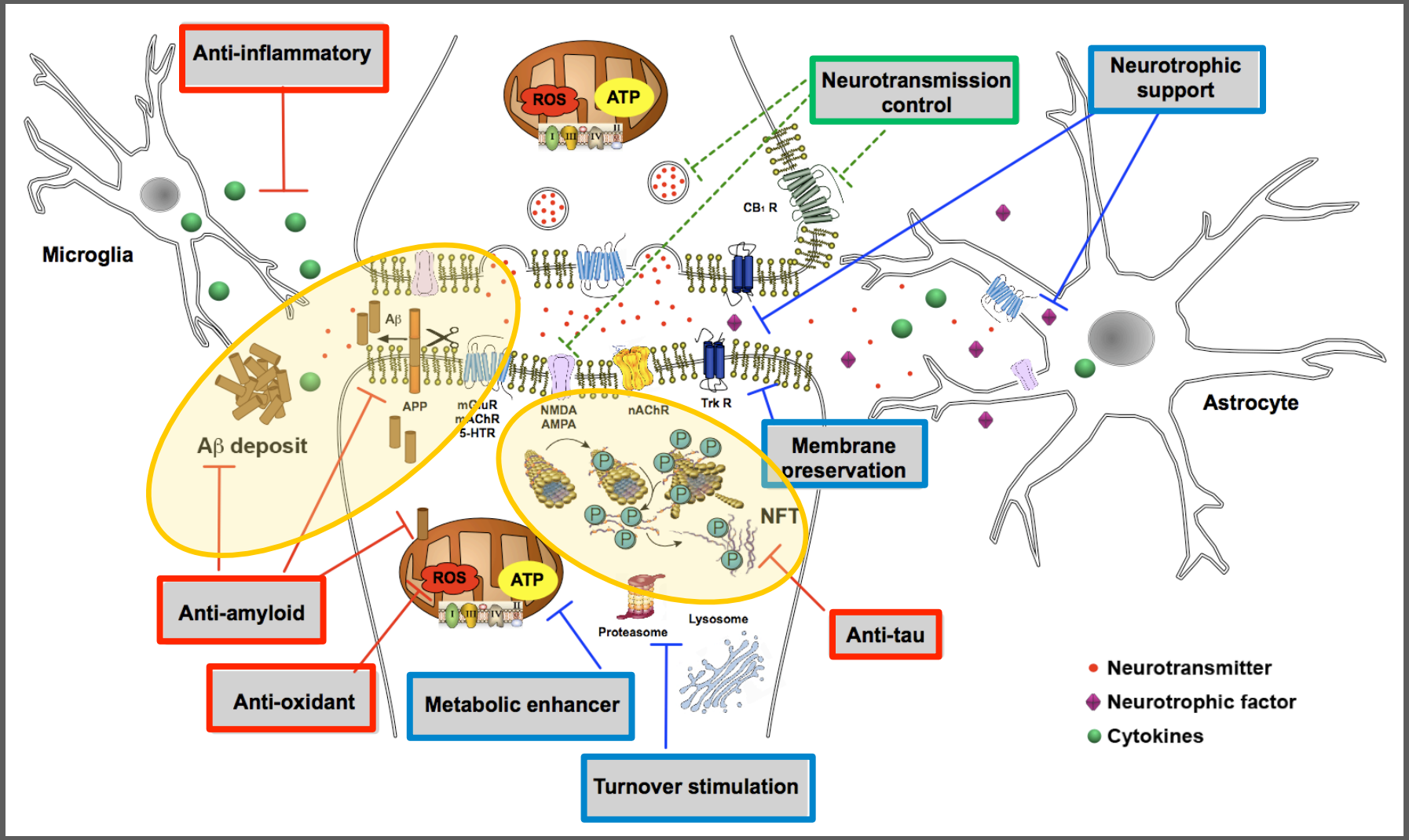
Alzheimer's disease

Most promising targets for drug development



Ref: Aso et al, Understanding Alzheimer's disease, 2013

Clinical trials focus on Abeta and Tau

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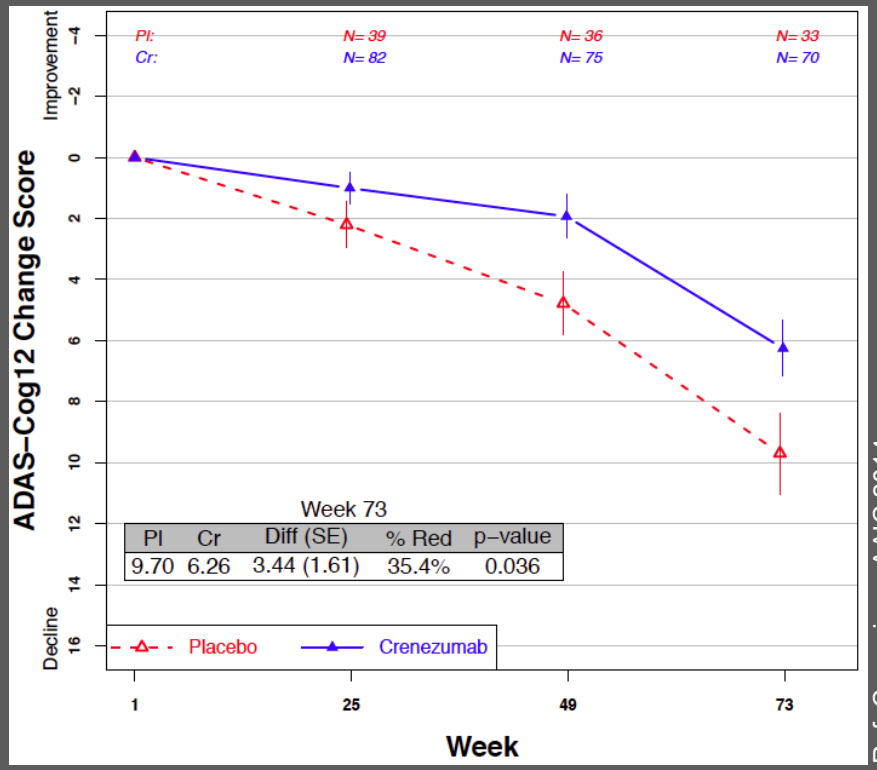
Recent achievements in Alzheimer's disease
Abeta pathway is confirmed

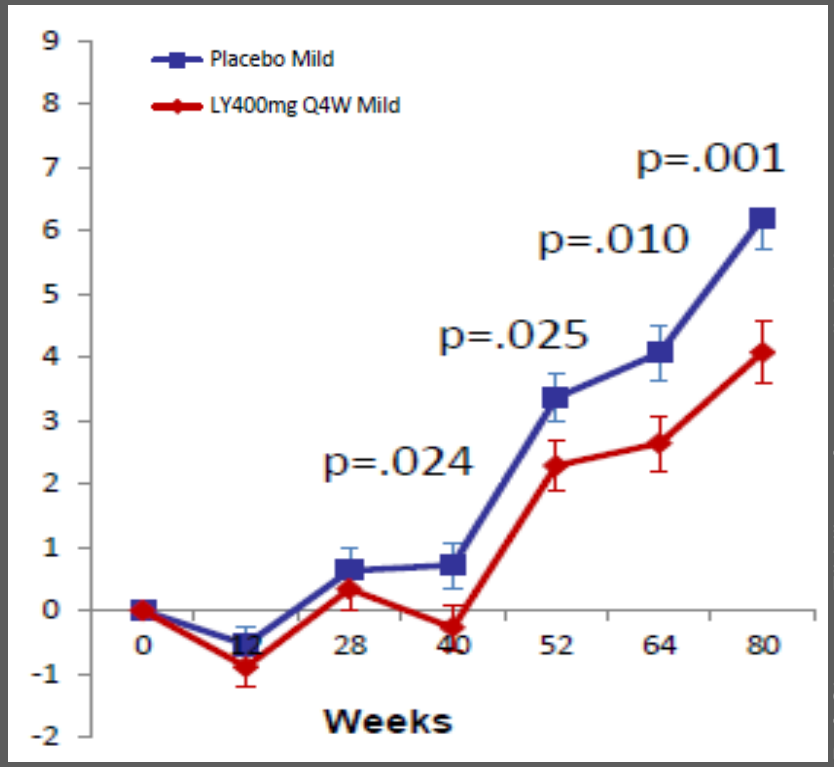
Slowing of cognitive decline is possible

Crenezumab ABBY phase 2
Change in ADAS-cog 12 in mild patients (MMSE 22-26)



Ref: Cummings, AAIC 2014

Solanezumab Expedition 1 and 2 phase 3 - pooled
Change in ADAS-cog 14 in mild patients (MMSE 20-26)



Ref: Siemers, Eli Lilly conference call 2012

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Path to the future - Alzheimer's prevention
Clinical trials in genetically defined populations

Protection from AD by Iceland gene mutation

A mutation in *APP* protects against Alzheimer's disease and age-related cognitive decline

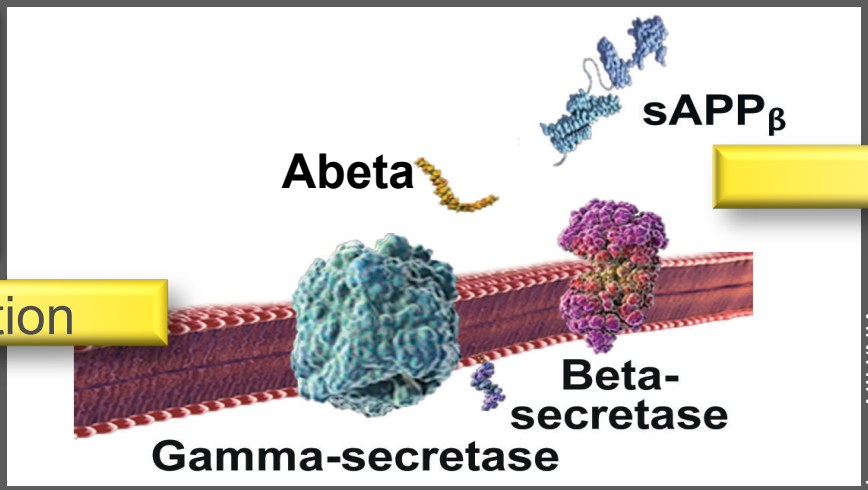
Thorlakur Jonsson[1], Jasvinder K. Atwal[2], Stacy Steinberg[1], Jon Snaedal[3], Palmi V. Jonsson[3,8], Sigurbjorn Bjornsson[3], Hreinn Stefansson[1], Patrick Sulem[1], Daniel Gudbjartsson[1], Janice Maloney[2], Kwame Hoyte[2], Amy Gustafson[2], Yichin Liu[2], Yanmei Lu[2], Tushar Bhangale[2], Robert R. Graham[2], Johanna Huttenlocher[1,4], Gyda Bjornsdottir[1], Ole A. Andreassen[5], Erik G. Jönsson[6], Aarno Palotie[7], Timothy W. Behrens[2], Olafur T. Magnusson[1], Augustine Kong[1], Unnur Thorsteinsdottir[1,8], Ryan J. Watts[2] & Kari Stefansson[1,8]

Ref: Nature 2012

Early onset Alzheimer's in people with genetic predisposition

- Columbia family clan: Paisa mutation (E280A PS1) leads to Abeta accumulation
- People with Down syndrome : Triple copy of APP gene leads to Abeta accumulation

Paisa mutation



3x

Image NIH/NIA

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Path to the future - Alzheimer's prevention

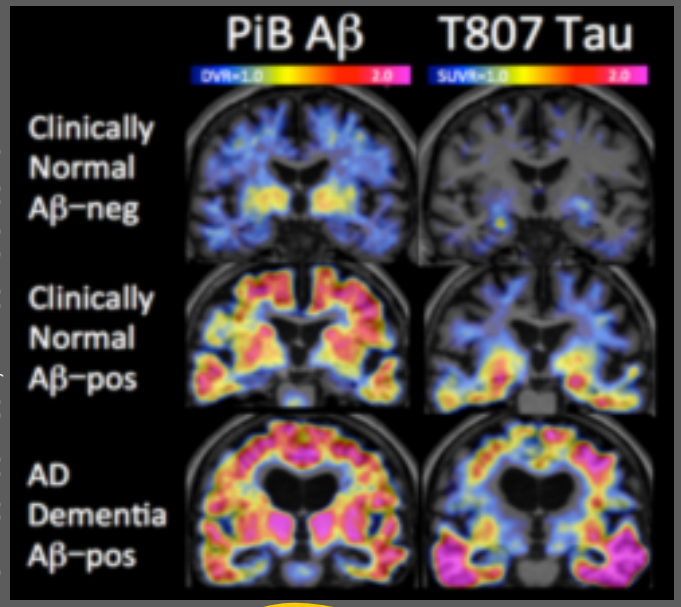
AD prevention trials targeting Abeta pathway

	API Trial	DIAN Trial	A4 Trial	API ApoE4 Trial
Study population	300 volunteers from kindred with PSEN1 mutation	240 volunteers from families with FAD mutation	1100 voluteers over 70 years old with amyloid in brain	1300 volunteers, age 60-75 with two copies of ApoE4
Expected time to onset	5 years	10-15 years	unknown	High probability to develop AD
Drugs tested	Crenezumab	Gantenerumab Solanezumab BACE - Inhibitor	Solanezumab	CAD106 BACE-inhibitor
Sponsor Consortium	NIH Banner AD Institute Genentech	NIA US-AD Association Roche Eli Lilly	NIH Private partnerships	NIH Banner AD Institute Novartis other foundations

A step closer to the future

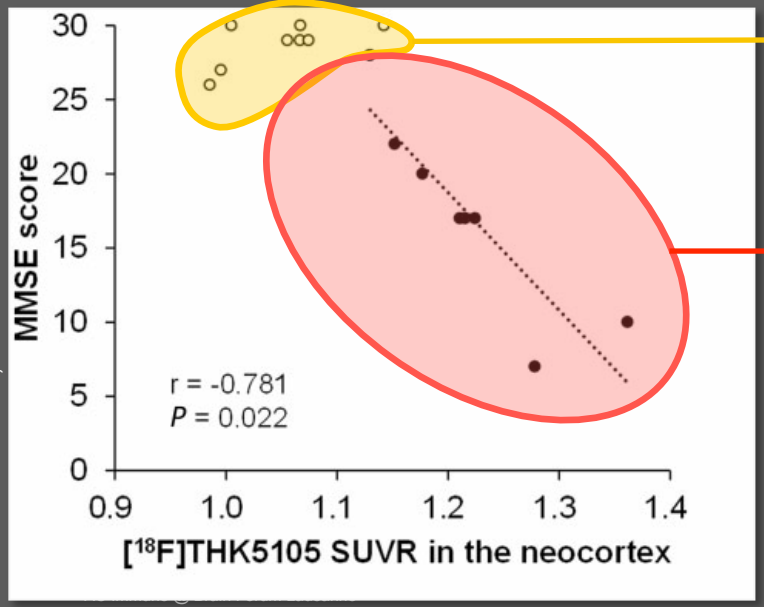
PET data confirm Tau as second important target

- Tau pathology spreads through the brain



Ref: Keth Johnson, HAI conference 2014

- Tau pathology correlates well with disease severity



Ref: Okamura et al, Brain 2014

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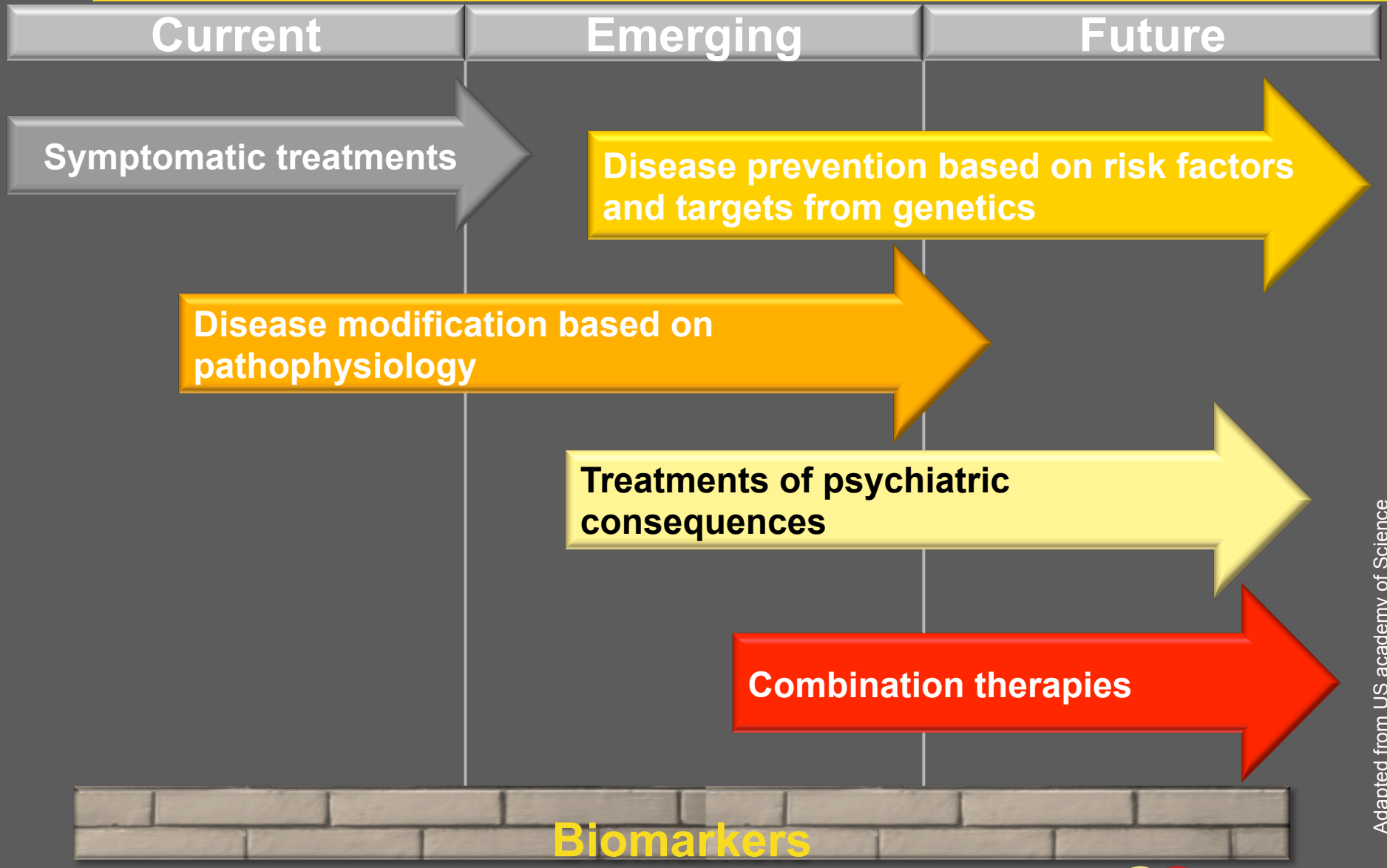
A step closer to the future
First-anti Tau agents in clinical trials

TARGET TYPE | THERAPY TYPE

Target Types	Timeline	Phase 1/2	Phase 1	Phase 2	Phase 2/3	Phase 3	Phase 4	Approved	Inactive	Discontinued	Not Regulated	Total
Amyloid-Related		1	8	12	4	3	0	0	3	12	0	43
Tau		0	3	0	0	1	0	0	1	3	0	8
Cholinergic System		0	1	2	0	1	0	4	5	11	0	24
Other Neurotransmitters		0	0	6	0	2	1	1	2	11	0	23
Cholesterol		0	1	0	0	0	1	0	1	0	0	3
Inflammation		0	2	3	3	1	0	0	1	8	0	18
Metals		0	0	1	0	0	0	0	0	1	0	2
Other		0	2	23	2	4	3	0	4	8	0	46
Unknown		0	0	6	0	1	1	0	3	3	0	14

Ref: Alzforum, October 2014

Alzheimer's disease drug development
Where we need to go



Adapted from US academy of Science

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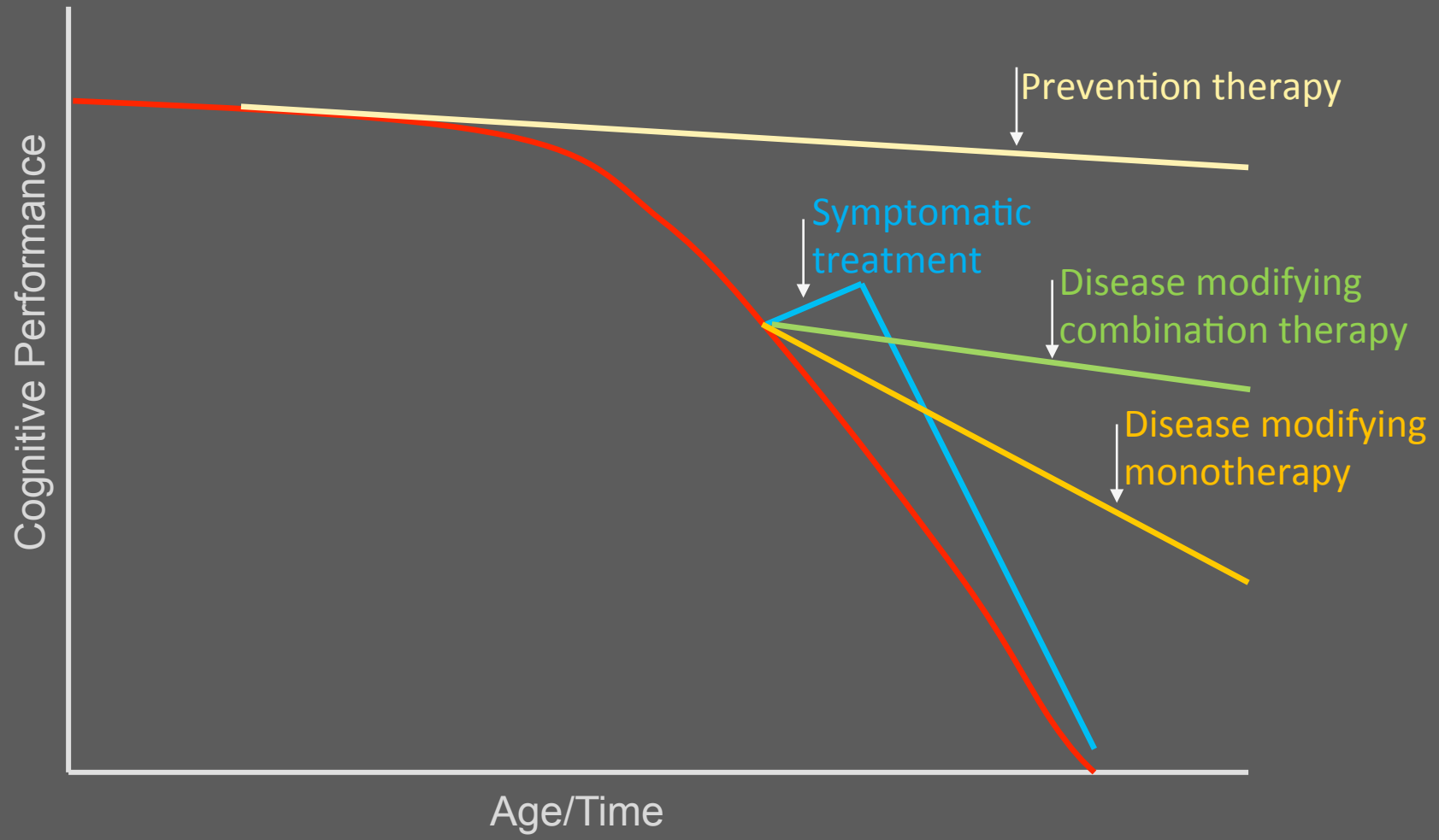
Emerging strategies
Combination therapy



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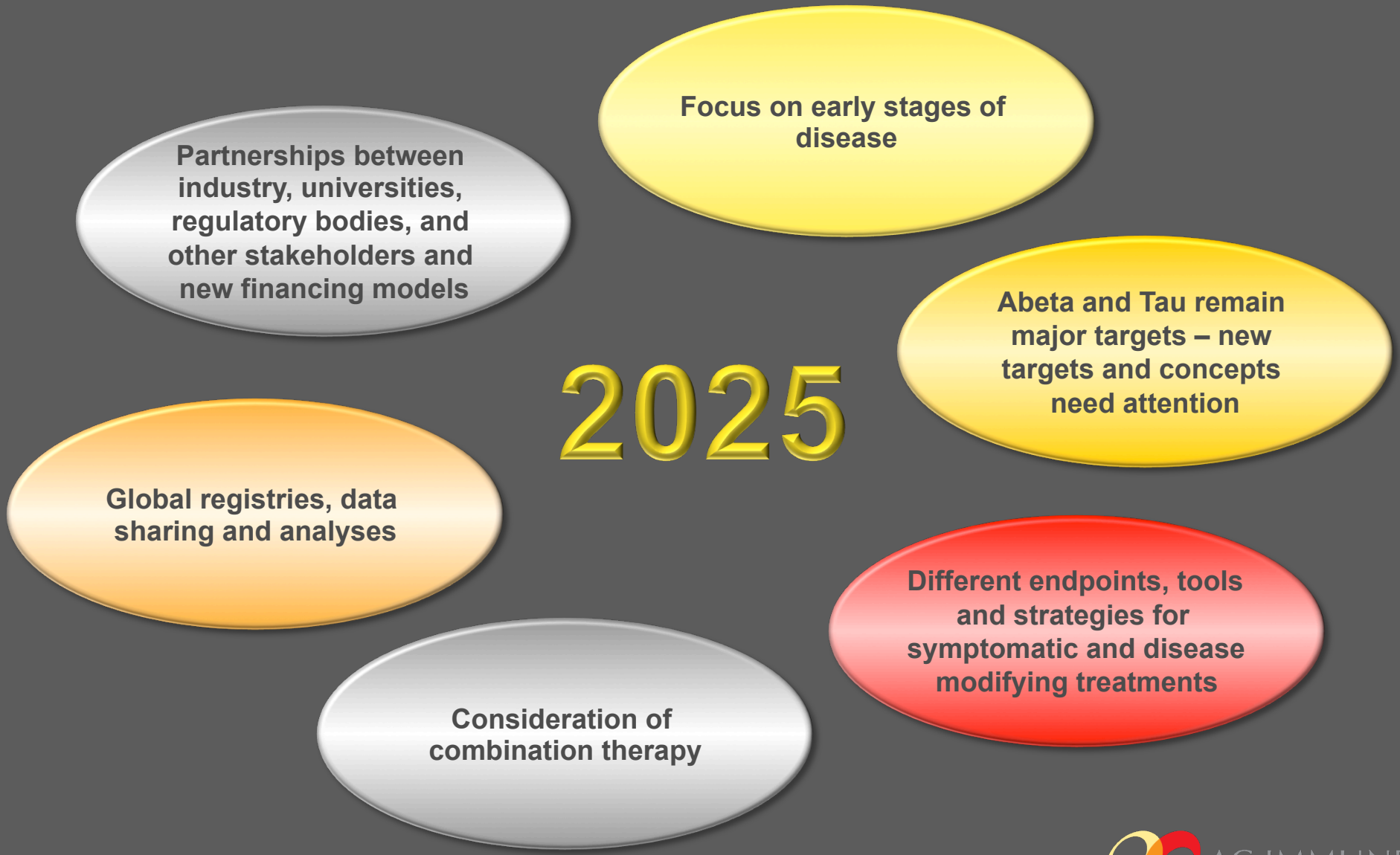
Regulatory agencies are vital stakeholders
Collaborative efforts to accelerate breaktrough therapies

- Support development and implementation of surrogate markers in clinical trials
- Allow early access to new medicines with highly positive Phase II/III results through conditional approval / adaptive licensing / Treatment IND
- Support approval of drugs based on a single (cognitive) endpoint in early disease
- Accelerate development of combination therapy through regulatory acceptance of appropriate preclinical and clinical safety data
- Encourage industry through longer market exclusivity
- Harmonize regulatory guidance for AD development

Key needs to find a cure for Alzheimer's before 2025



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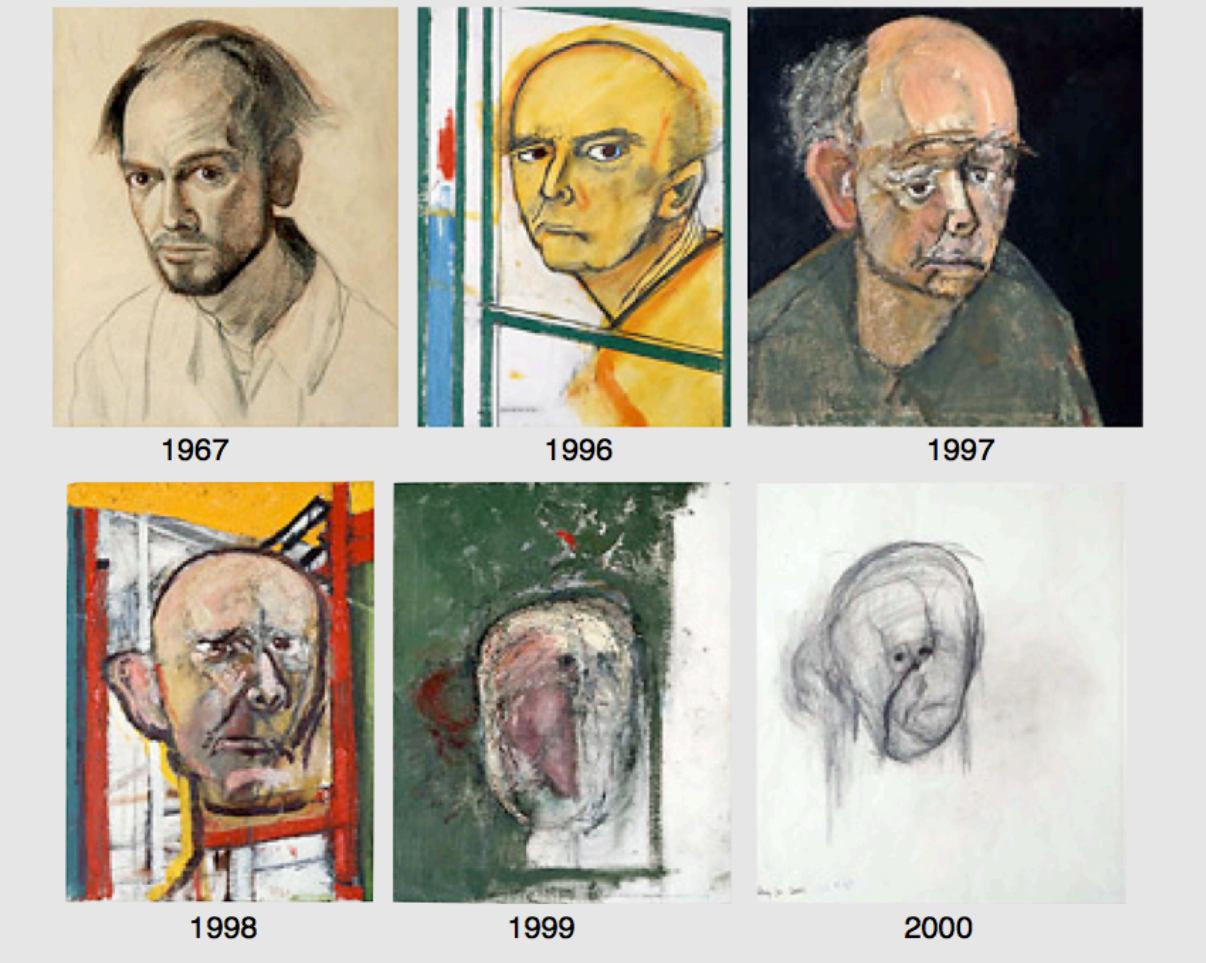
William Utermohlen - artistic decline through Alzheimer's



"He died in 2007, but really he was dead long before that,"
Patricia Utermohlen, GV Art Gallery London, January 2012

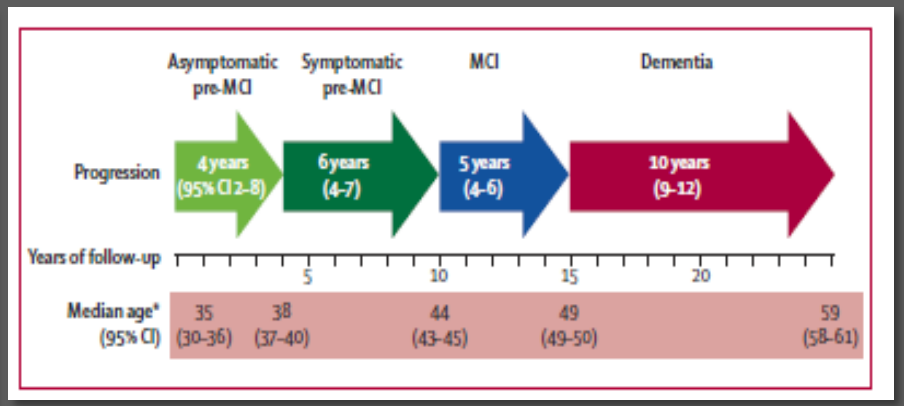
Back up

Path to the future – Alzheimer's prevention
API ADAD prevention trial

Colombian family clan at the forefront of research

- Groundbreaking first ever prevention stuy in healthy individuals with genetic predisposition
- Unique opportinity to study prevention and treatment in defined population
- Phase II study with 300 participants (200 mutation carriers/100 non-carriers, double-blind, placebo controlled)
- Private Public Partnership (NIH, Banner Alzheimer Institute, Genentech and AC Immune)
- Study start in December 2013

New York Times Alzheimer section



Ref: Lancet Neurology Lacosta-Baena 2011

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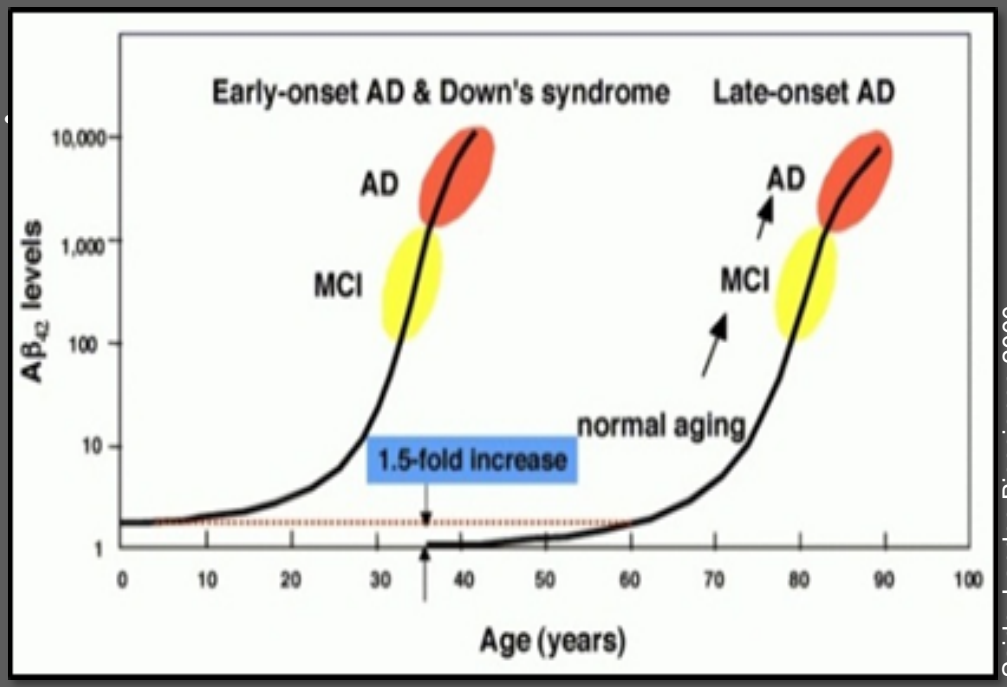
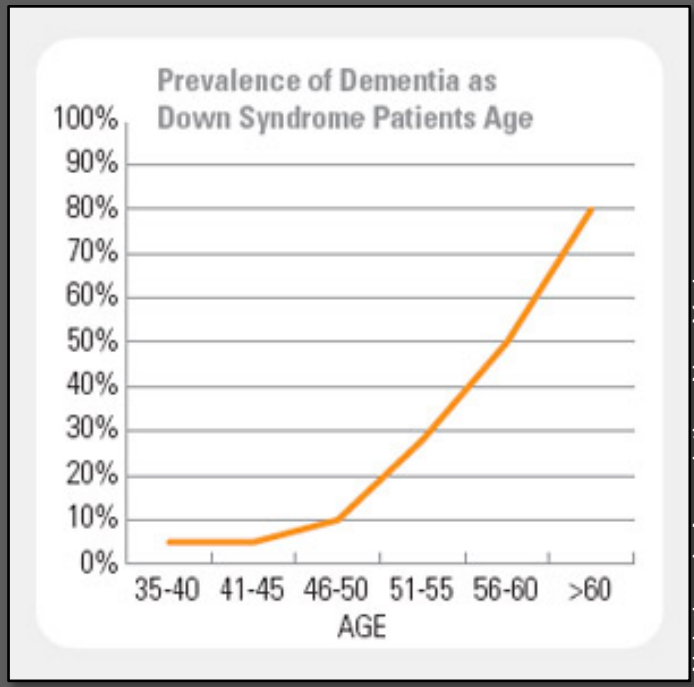
Path to the future - Alzheimer's Prevention
Prevention trial in population with Down Syndrome

Down Syndrome People with genetic predisposition for Alzheimer's

- World first clinical trial for vaccine targeting Alzheimer's disease in people with Down Syndrome
- Clincial study, placebo controlled, double blind
- Private public partnership (AC Immune, University of San Diego's Down Syndrome Center for Research and Treatment, NIH, LuMind Foundation and Research Down Syndrome)



Saido, Landes Bioscience 2000



Alzheimer's Association, New York

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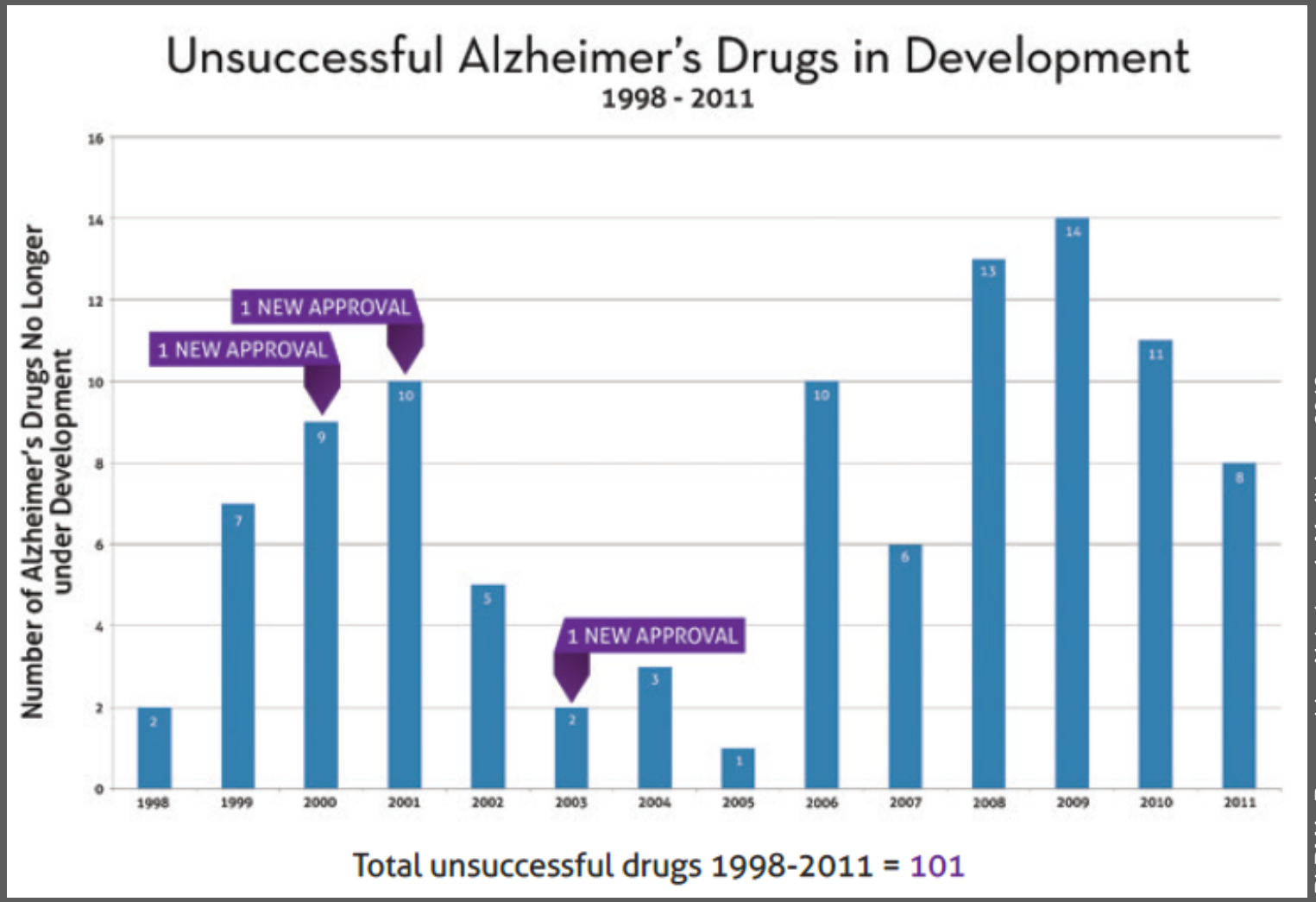
Alzheimer's disease
History of failure in drug development

No new drug approved since more than 10 year's



PhRMA, Researching Alzheimer's Medicines, 2012

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Path to the future - Alzheimer's Prevention
API ADAD prevention trial

Clinical trial	• Groundbreaking first everAD prevention trial in cognitively healthy individuals who will develop AD because of their genetic predisposition • Test the amyloid hypothesis • Phase II study of 300 subjects
Study partners	• Banner Alzheimer Institute, Arizona USA • US National Institutes of Health (NIH) • University of Antiochia, Colombia • Genentech – developer of Crenezumab • AC Immune – discoverer of Crenezumab
Participant characteristics	• 30 years and older being in preclinical phase of AD • No cognitive impairment
Study objectives	• Efficacy (API composite cognitive test battery), Safety and tolerability and biomarkers • Time to onset of Alzheimer's disease
Study timeline	• First patients received dose in Dec. 2013 • Interim analysis after 2 years of treatment • 2020: Study completion

Path to the future - Alzheimer's Prevention
Prevention trial in population with Down Syndrome

Study description	• World first clinical trial for vaccine targeting Alzheimer's disease in people with Down syndrome • Test the Abeta hypothesis • Clinical study, double blind, placebo-controlled
Study partners	• AC Immune • University of San Diego's Down Syndrome Center for Research and Treatment • US National Institutes of Health (NIH) • LuMind Foundation and Research Down Syndrome
Participant characteristics	• 35-45 years old people with Down syndrome
Study objectives	• Safety and tolerability • Effect on induction of anti-Abeta antibodies • Clinical and cognitive measures • Biomarkers to study Abeta brain and CSF load
Study timeline	• Recruitment of patients planned to start 2015 • 6 months treatment + 12 months safety follow up

Emerging strategies
New hot targets

- Neuroinflammation
- Mitochondrial dysfunctions
- Epigenetics: HDAC inhibitors, miRNA modulators
- Neurogenesis
- Stem cells
- Neurotrophins
- Endoplasmatic reticulum stress
- Unfolded protein response
- Cell cycle dysfunctions