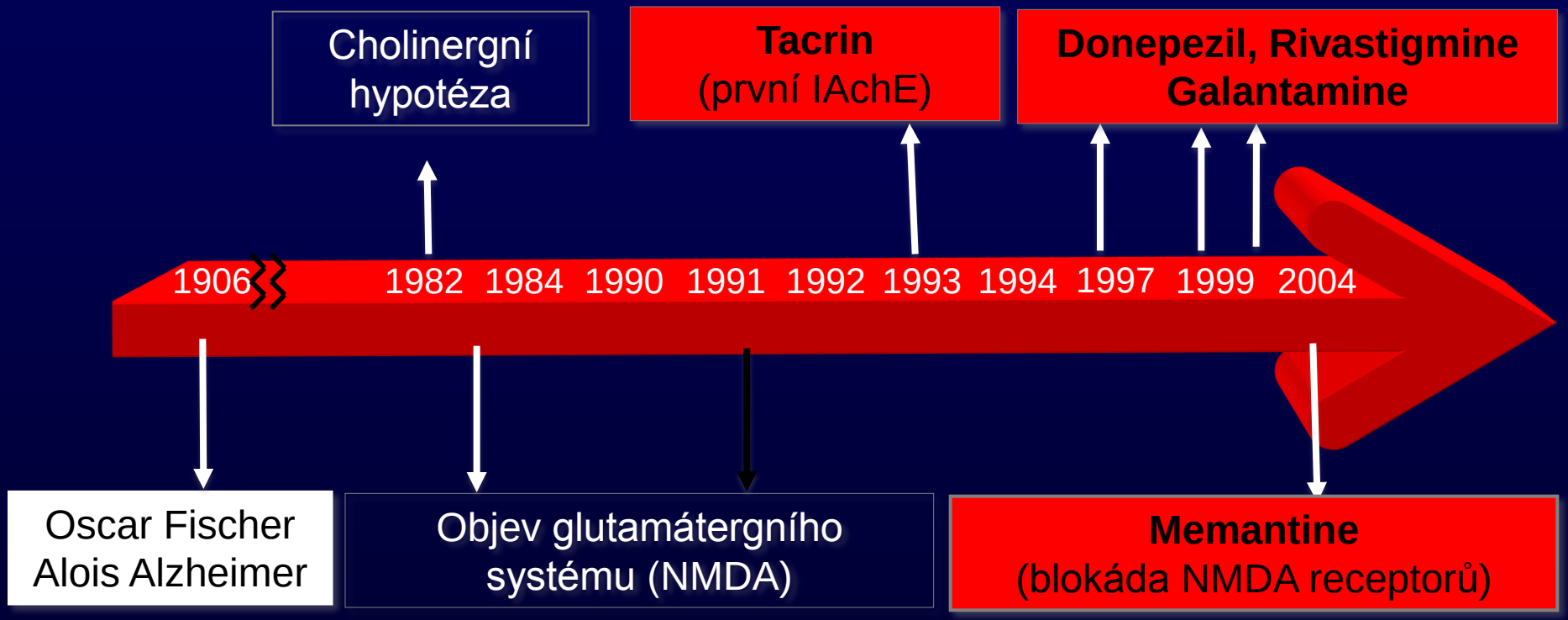
Nové možnosti léčby Alzheimerovy choroby jsou na dohled

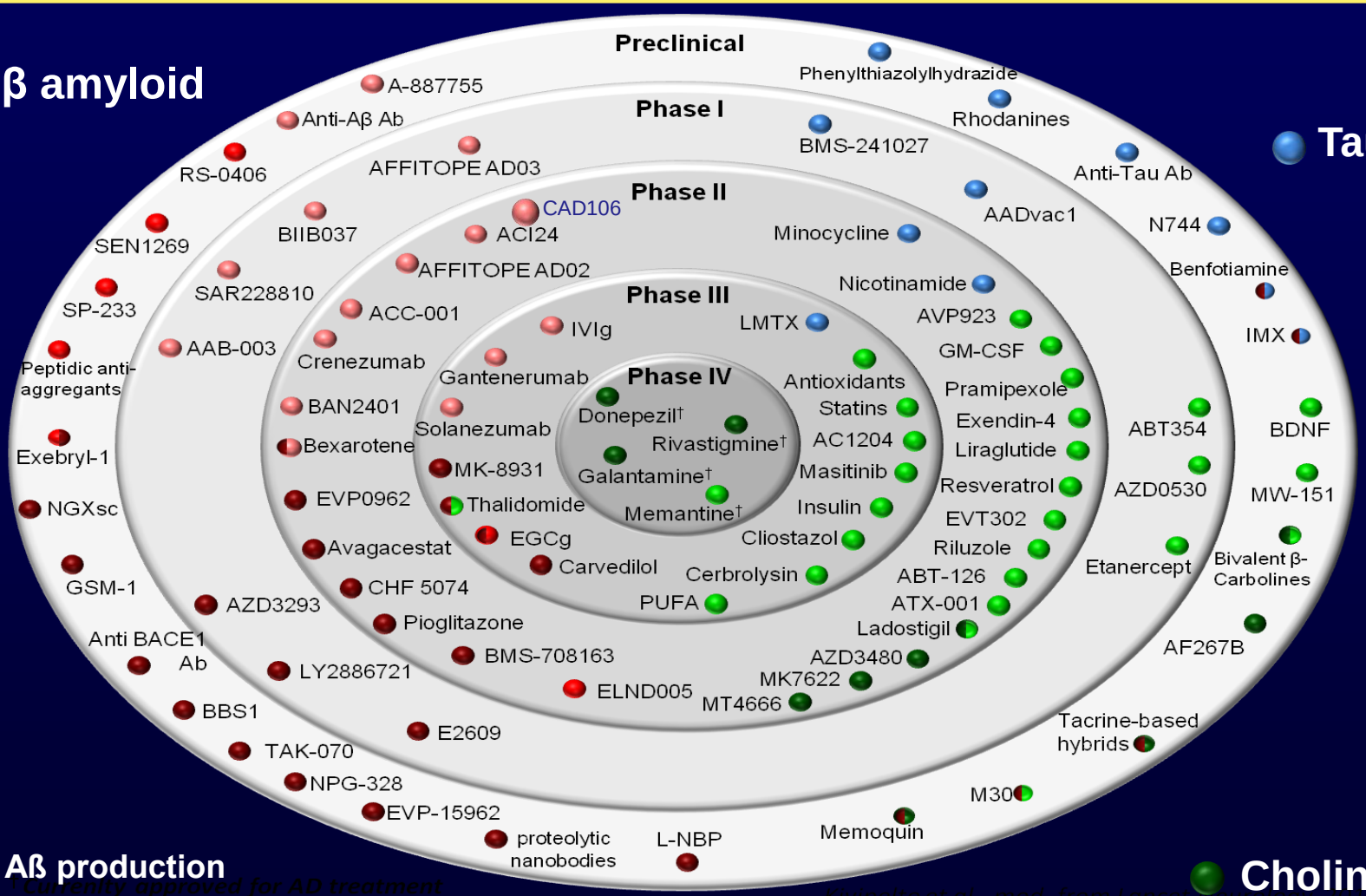
Prof. MUDr. Jakub Hort, Ph.D.

Neurologická klinika UK, 2. LF a FN Motol
Mezinárodní centrum klinického výzkumu Brno

Žádné nové léky od roku 2004



Vývoj nových léků – tolik zklamání!



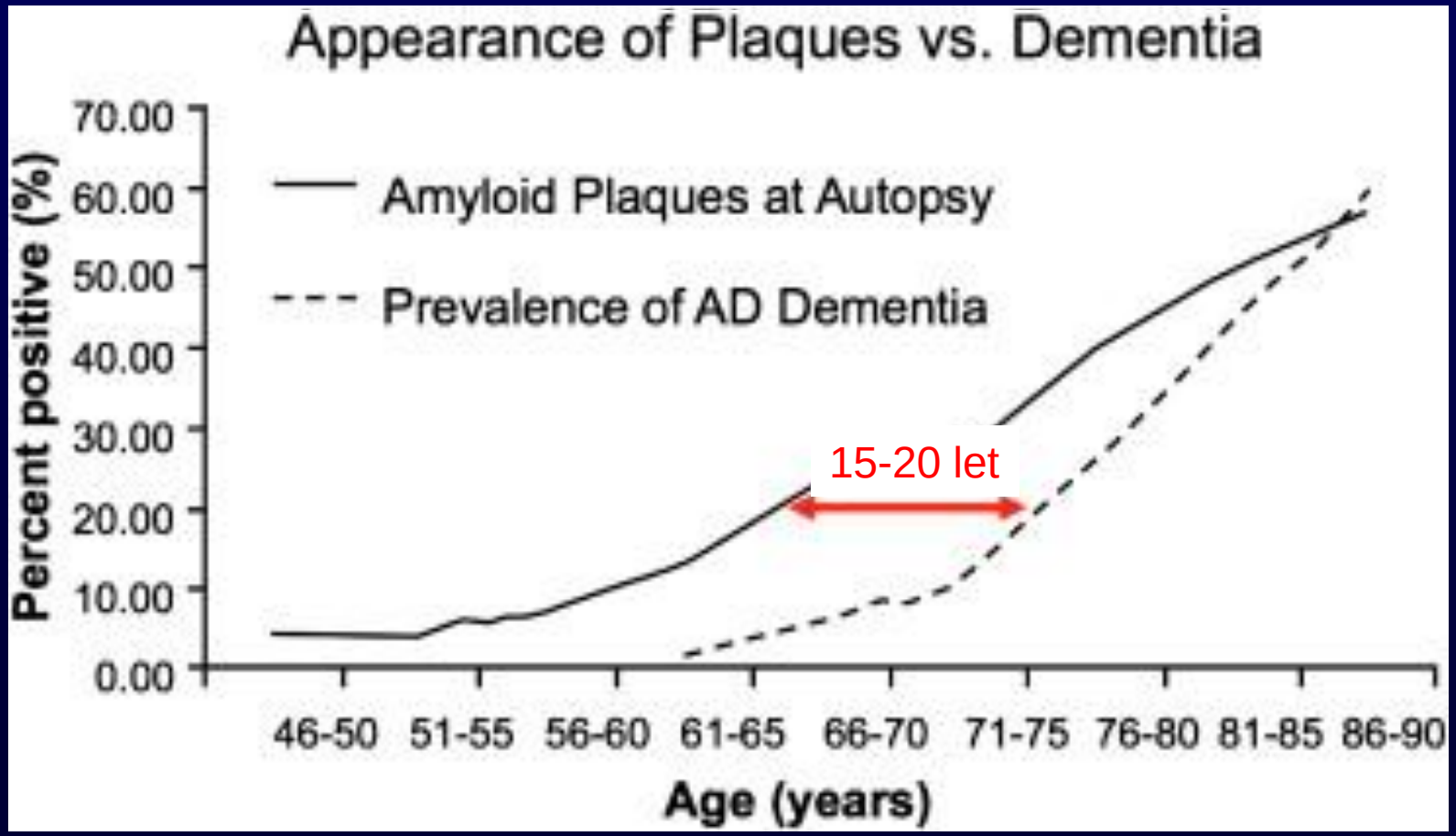
Mangialasche et al, modified 2013 from Lancet Neurology, 2010

Příčiny selhání

- Provedení klinických studií
  - špatní pacienti (neměli Alzheimera)
  - podávání v příliš pokročilé fázi onemocnění
  - člověk není potkan (preklinická fáze – fáze I, II)
- Neúčinné molekuly
- Nevhodné cíle (nebo nedostatečný target engagement)

Selkoe, 2012, Korczyn et al., 2012, Giaccobini et al., 2013, Hort et al., 2013

Amyloidové plaky versus demence

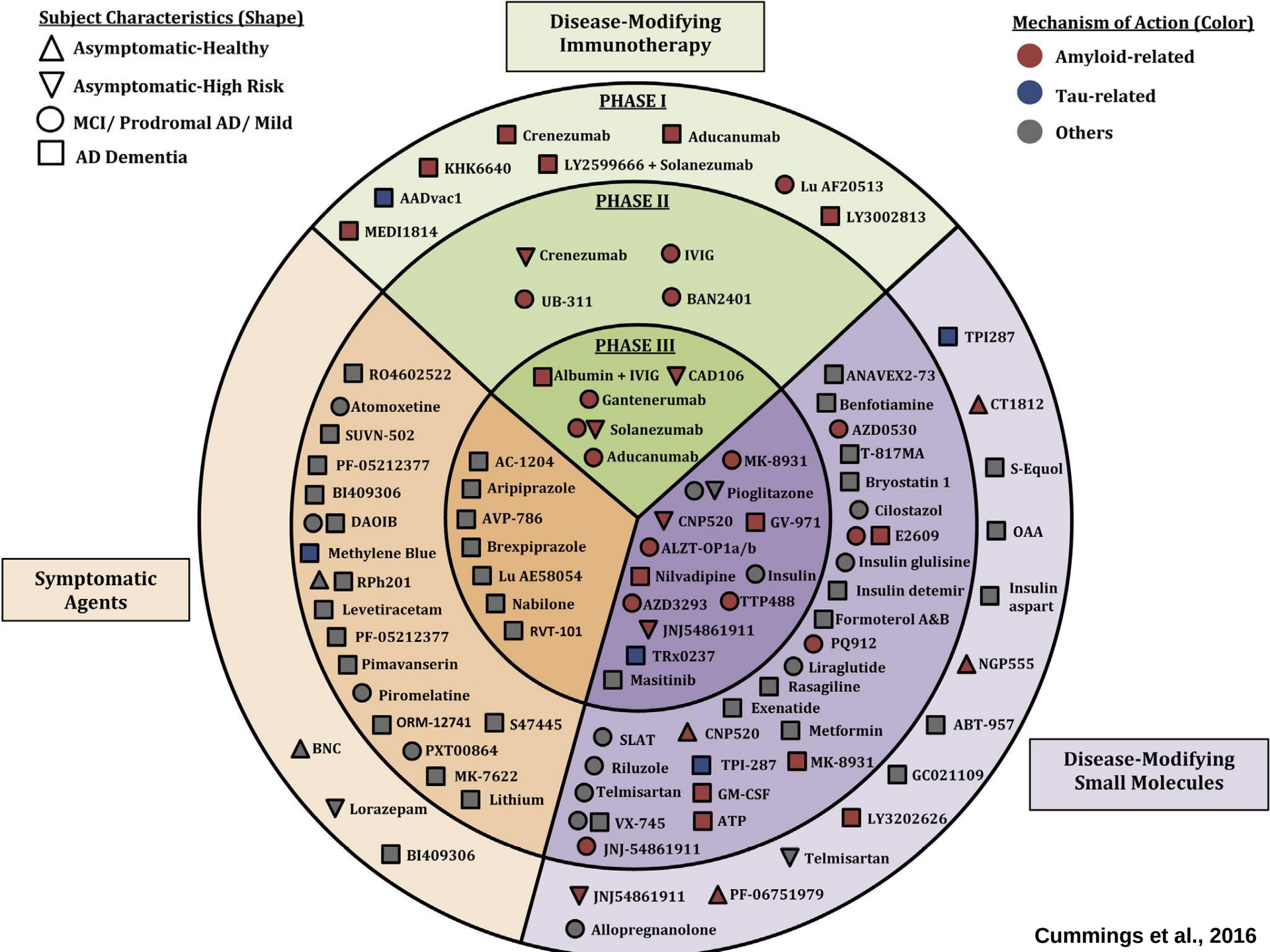


Sperling R et al. (2011) Alzheimers Dement 7, 280-282

Prevence

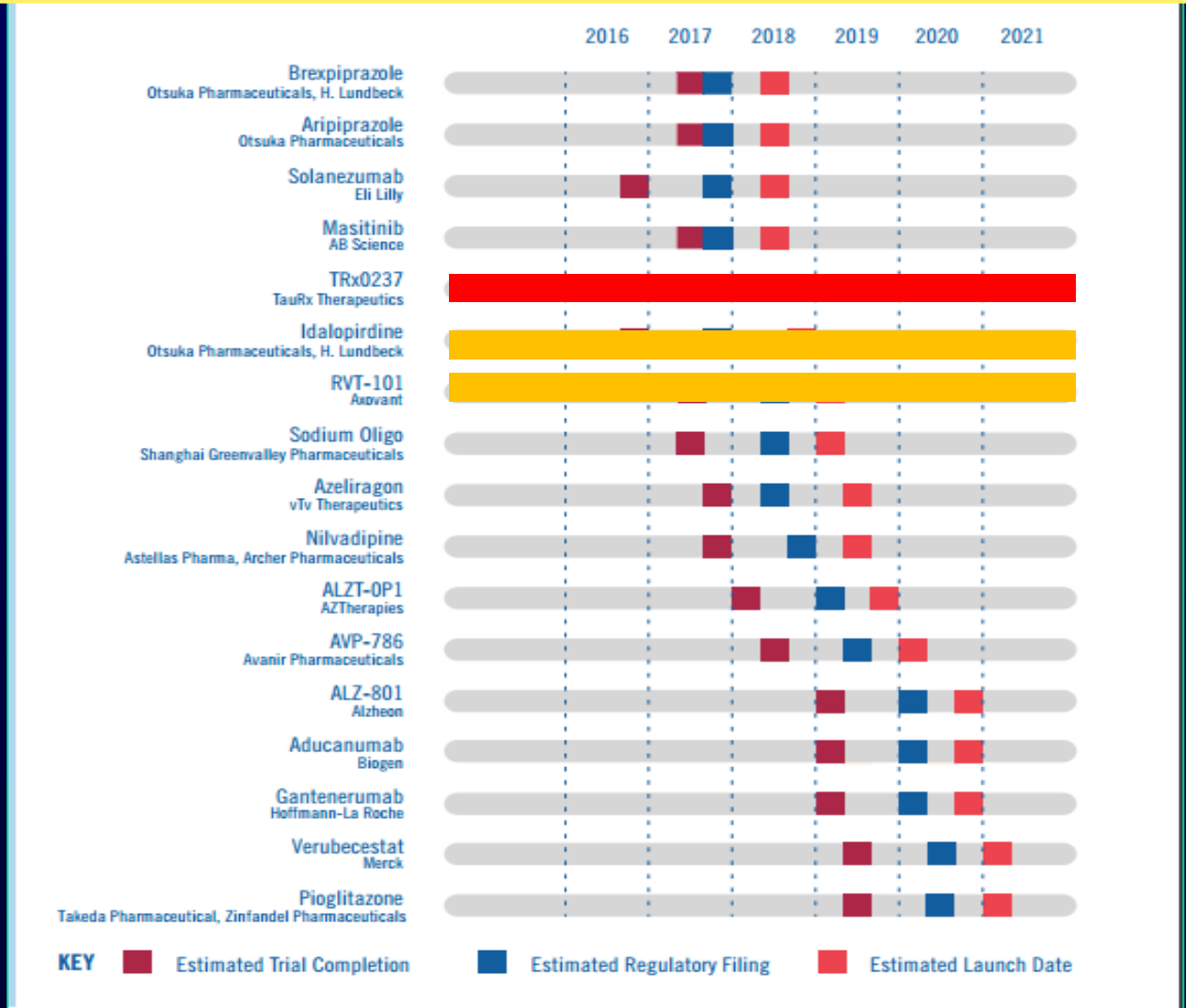
Sponsoring group	Subjects (number proposed)	Special conditions	Rationale for subject selection	Drug intervention	Trial duration	Outcome variable(s)
Alzheimer's Prevention Initiative (API)[9,10]	Asymptomatic subjects with mutations in PS1 (100 drug; 100 placebo)	PS1-positive subjects within 10 years before apparent cognitive decline	Excess $A\beta_{42}$ levels predispose to early-onset AD	Crenezumab	5 years	PET-fibrillar Aβ, PET-FDG, structural MRI and clinical end point biomarkers accepted as indicators of AD progression and an untested composite of five cognitive tests not specified[9,10]
Dominantly Inherited Alzheimer Network (DIAN)[6]	Asymptomatic subjects at-risk for familial AD (mutations in APP, PS1 and PS2) (160)	Subjects within 15 years of predicted AD onset	Confirmed family pedigree for autosomal dominant AD	Solanezumab and gantenerumab	5 years	Neuropathological biomarkers to validate target effects of drug interventions and an undisclosed cognitive end point[6]
Anti-amyloid treatment in asymptomatic AD (A4)[11]	Elderly asymptomatic and symptomatic subjects (500 drug; 500 placebo)	Subjects positive for brain amyloid with PET imaging	Drug intervention prior to irreversible neuropathological damage to neurons	Solanezumab	3 years	The untested ADCS–PACC outcome includes the Free and Cued Selective Reminding Test, the Logical Memory IIa, Digit Symbol and Mini Mental State Exam[6,11].
Down Syndrome Biomarker Initiative' (DSBI)[12]	Subjects with Down's syndrome (12)	APP trisomy	Development of brain amyloid plaques and neurofibriallary tangles by age 30 years and increased lifetime risk (75%) for AD	Not specified[12]	3 years	Not specified[12]

Becker et al., Nature Rev Drug Discov, 2014



Cummings et al., 2016

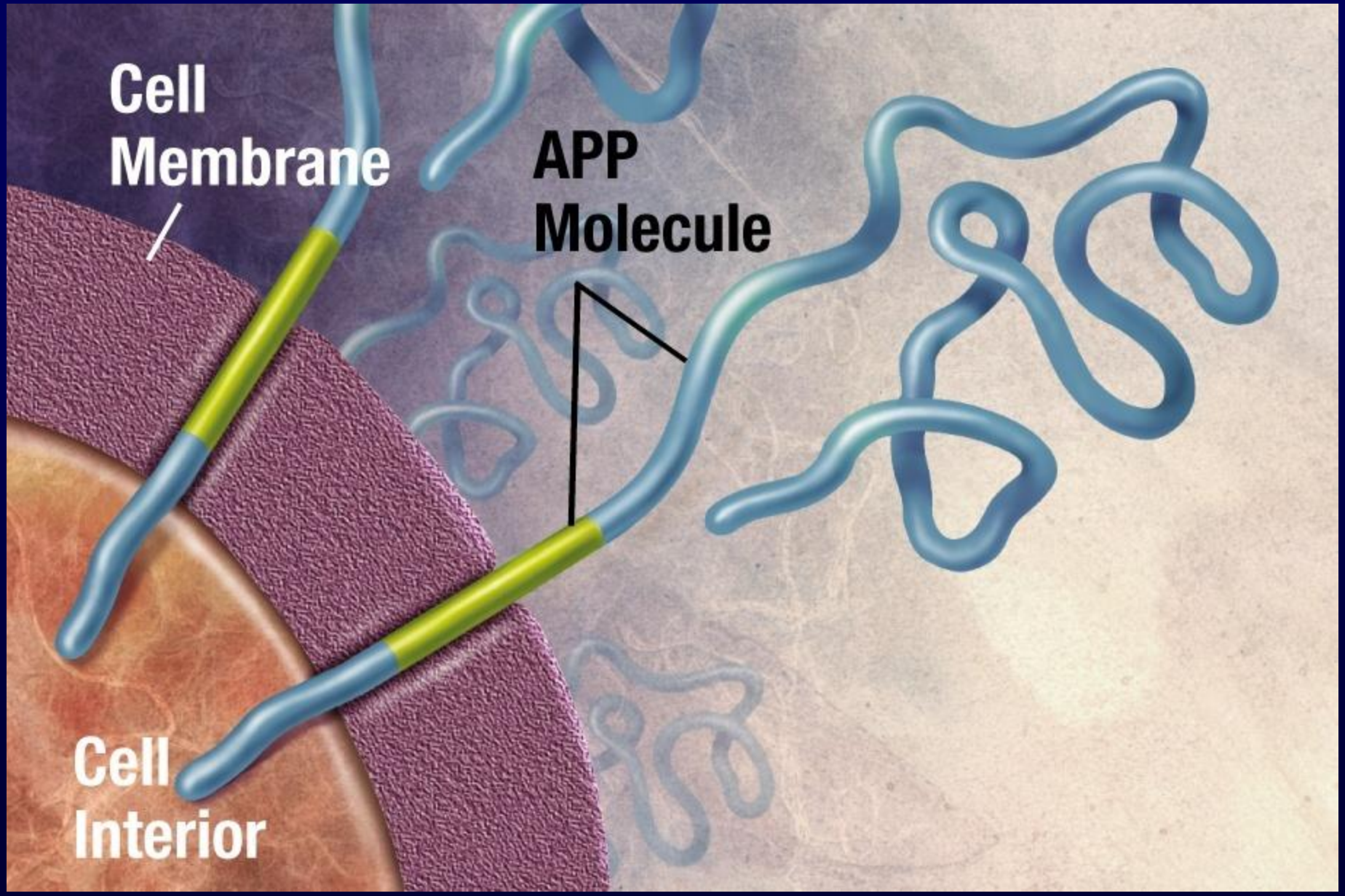
Výhledy nové léčby do roku 2021

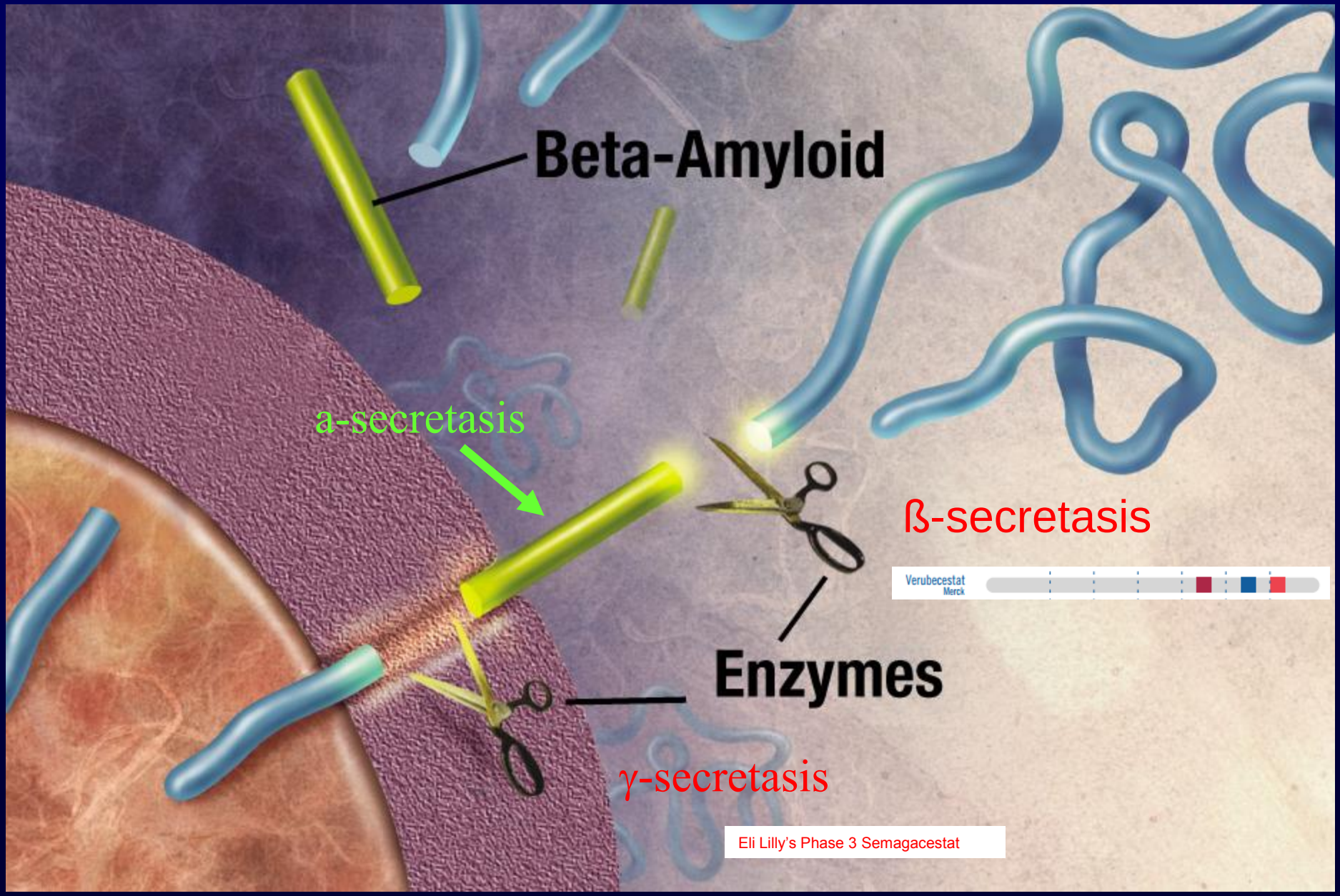


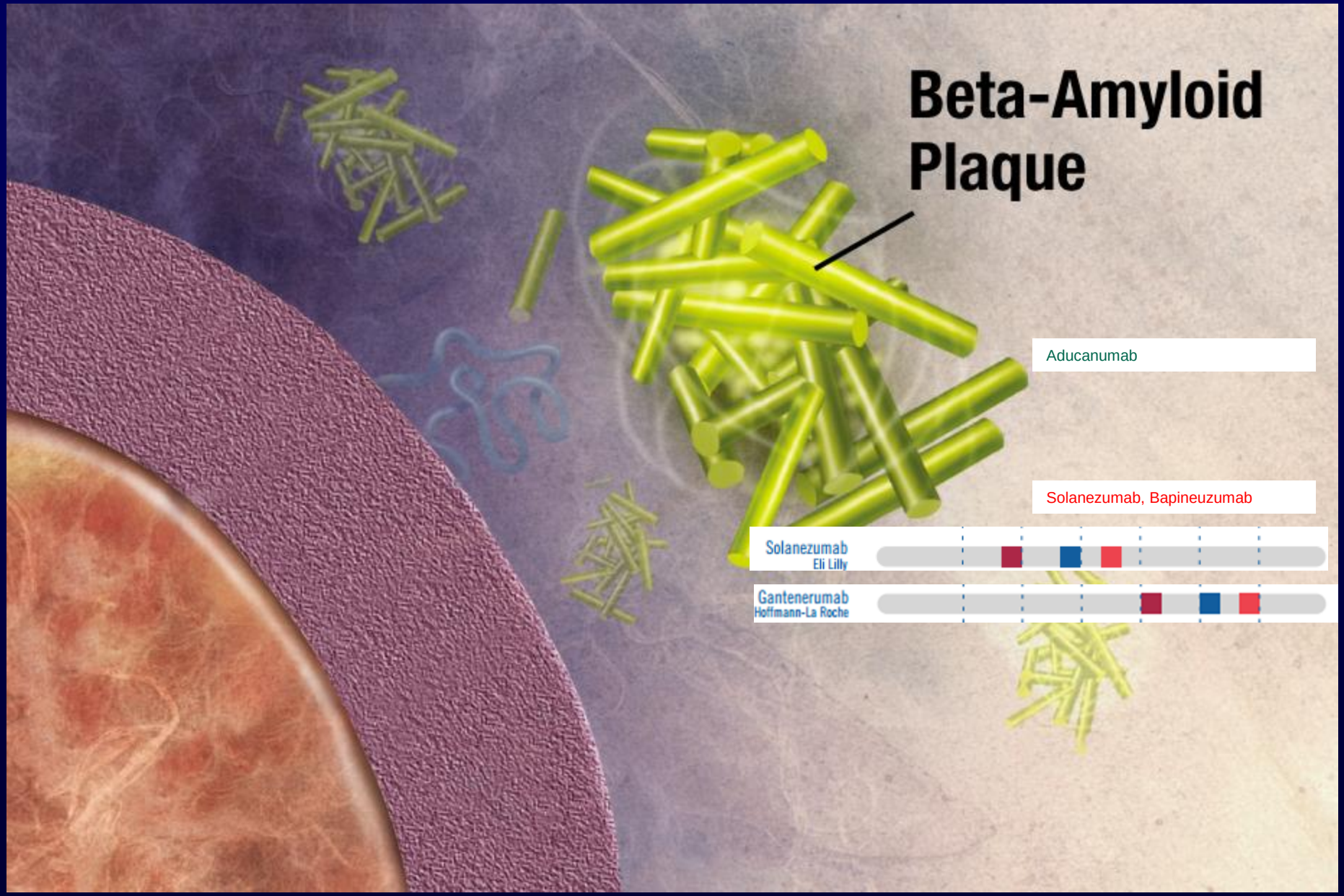
Us4gainst Alzheimer's

1) Postupy proti beta-amyloidu

- Inhibice produkce Aβ (beta a gama sekretáza)
- Zvýšení odstraňování Aβ (aktivní a pasivní imunizace)
- Inhibice produkce toxických (mono,oligo) forem Aβ
- Inhibice glutaminyl-cyklázy (seeds pro tvorbu plak)


Cell
Membrane
APP
Molecule
Cell
Interior


Beta-Amyloid
a-secretasis
ß-secretasis
Verubecestat
Merck
Enzymes
γ-secretasis
Eli Lilly's Phase 3 Semagacestat



Wisniewski, Konietzko, 2008

Nové postupy – nové problémy

Inhibitory gama sekretázy a BACE

- Inhibitory gama sekretázy – 2. krok štěpení
  - vedlejší účinky (zhoršení kognice, rakovina kůže, infekce)
  - bylo by předčasné tento přístup opustit

  (modulátory gama sekretázy – tvořen kratší, méně toxický Aβ)

- BACE 1 – 1. první krok štěpení APP
  - exprimovaná v neuronech, odstranění mnoha fyziol. substancí
  - inhibice navodí alternativní metabolismus APP s tvorbou peptidů, které na rozdíl od Aβ nejsou na synapsích škodlivé
  - fáze III, dobrá snášenlivost

Doody et al., 2013, Hajos et al., 2013

ARIA (amyloid-related imaging abnormalities)

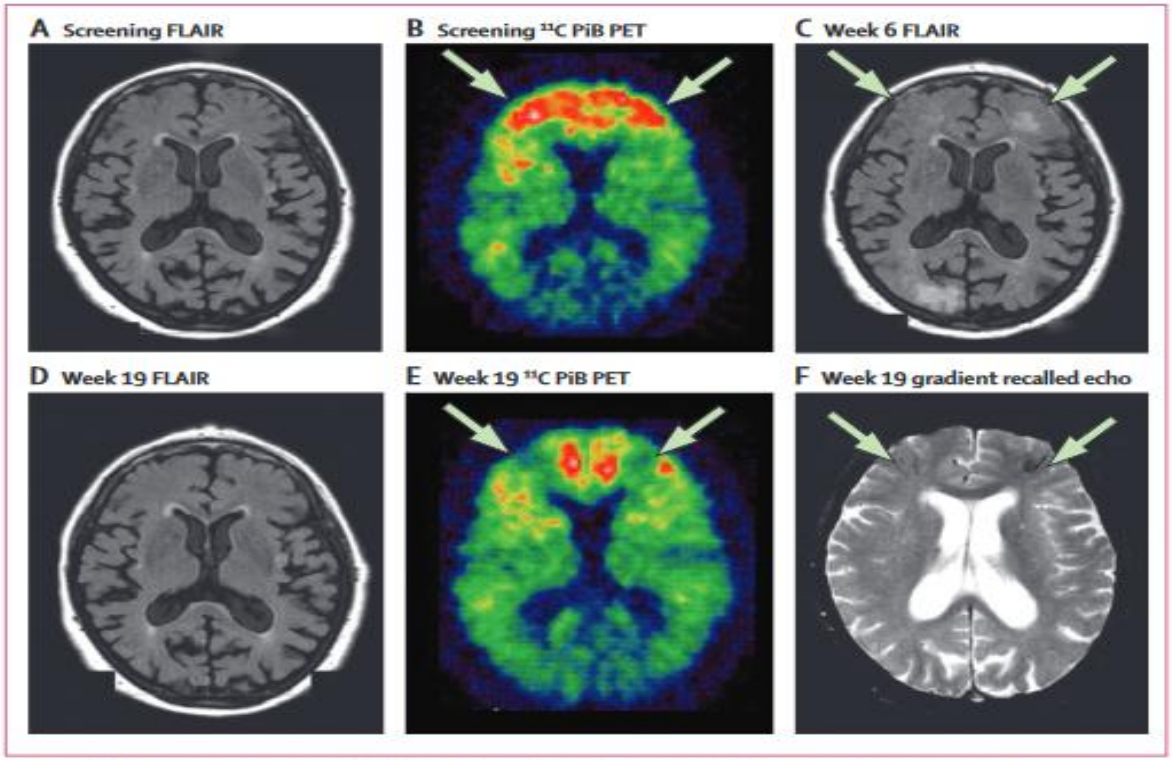


Figure 4: **MRI and ¹¹C PiB PET scans of an *APOE* ε4 heterozygote given bapineuzumab (2·0 mg/kg)**
This patient was one of two who had ARIA-E in the 202 study. This patient had ¹¹C PiB PET imaging soon after the onset of the ARIA. Baseline FLAIR image without evidence of ARIA-E (A). FLAIR sequence obtained at week 6 (C) shows bifrontal parenchymal hyperintensity (arrows; ARIA-E) which resolved by week 19 (D). Additionally, week 19 gradient echo T2*-weighted sequence (F) shows the development of bifrontal microhaemorrhages (ARIA-H; arrows) not present on previous images (not shown). A corresponding week 19 ¹¹C PiB scan (E) shows reduced ¹¹C PiB uptake (arrows) compared with that at baseline in regions with ARIA-E and ARIA-H (arrows; B). FLAIR=fluid attenuation inversion recovery. ¹¹C PiB=¹¹C Pittsburgh compound B. ARIA-E=amyloid-related imaging abnormalities thought to be parenchymal vasogenic oedema and sulcal effusions. ARIA-H=amyloid-related imaging abnormalities thought to be a result of microhaemorrhages and haemosiderosis.

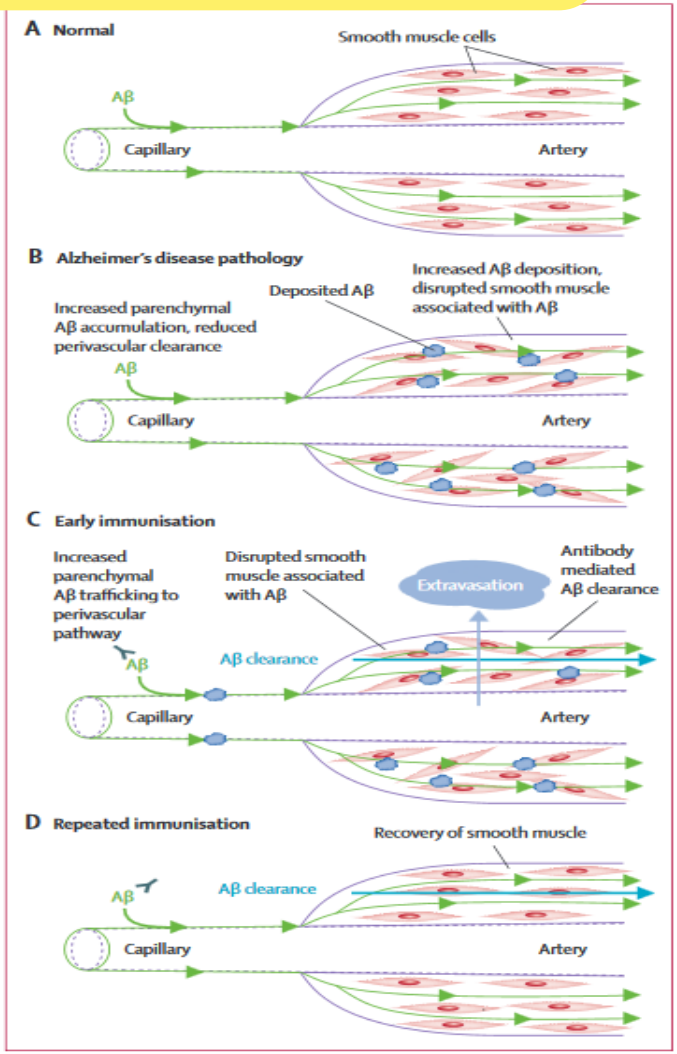


Figure 5: **Model of ARIA mechanisms related to vascular amyloid clearance with anti-Aβ therapy**

Sperling et al., 2012

Monoklonální protilátky

	Manufacturer	Epitope	Origin	Isotype	Target	Possible mechanism of action	Outcomes in latest stage trial	Amyloid biomarker inclusion criteria in trials	Trials planned or in progress	Rate of amyloid-related imaging abnormalities
Solanezumab (NCT0760005, NCT01900665)	Eli Lilly	Mid-domain	Humanised	IgG1	Soluble, monomeric, non-fibrillar Aβ	Sequestration of soluble monomeric Aβ	Negative clinical outcomes in two phase 3 trials in mild-to-moderate Alzheimer's disease; possible slowing of cognitive decline in mild disease	None	Phase 3 trials underway in mild, preclinical, and autosomal-dominant Alzheimer's disease	Low
Bapineuzumab (NCT00575055, NCT00574132)	Pfizer/Johnson & Johnson	N-terminus	Humanised	IgG1	All forms of Aβ (fibrillar, oligomeric, monomeric)	Microglia-mediated clearance	Negative clinical outcomes in two phase 3 trials despite significant decrease in amyloid PET and phosphorylated tau concentrations in cerebrospinal fluid	None	..	Related to dose and *APOE* ε4 carrier status
Crenezumab (NCT 01397378, NCT01723826, NCT01998891)	Roche/ Genentech	Mid-domain	Humanised	IgG4	All forms of Aβ (fibrillar, oligomeric, monomeric)	Microglia-mediated clearance	Negative clinical outcomes in phase 2 trials in mild-to-moderate Alzheimer's disease; possible cognitive slowing in mild disease in patients given high doses	None in ABBY trial; amyloid PET in BLAZE trial	Phase 3 trial in autosomal-dominant Alzheimer's disease underway	Low
BAN2401 (NCT01767311)	Eisai/Biogen	N-terminus	Humanised	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	No phase 2 trials yet completed	Amyloid PET	Phase 2 trial underway in mild cognitive impairment	..
Gantenerumab (NCT01224106, NCT02051608)	Roche/ Genentech	N-terminus and mid-domain	Human (phage display library and affinity maturation)	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	Negative clinical outcomes in phase 3 trial for prodromal Alzheimer's disease	Cerebrospinal fluid Aβ	New phase 3 trial in planning phase	Related to dose and *APOE* ε4 carrier status
Aducanumab (NCT02484547, NCT02477800)	Biogen/ Neurimmune	N-terminus	Human (RTM)	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	Dose-dependent decrease in amyloid PET and cognitive decline in early Alzheimer's disease (mild cognitive impairment and mild disease) in interim analysis of phase 1b trial	Amyloid PET	Phase 1 trial in prodromal or mild Alzheimer's disease and phase 3 trial of early disease underway	Related to dose and *APOE* ε4 carrier status

Aβ=amyloid β. ..=not applicable. RTM=reverse translational medicine.

Table: Anti-amyloid monoclonal antibodies in clinical development

Scheltens et al., 2016

ARTICLE

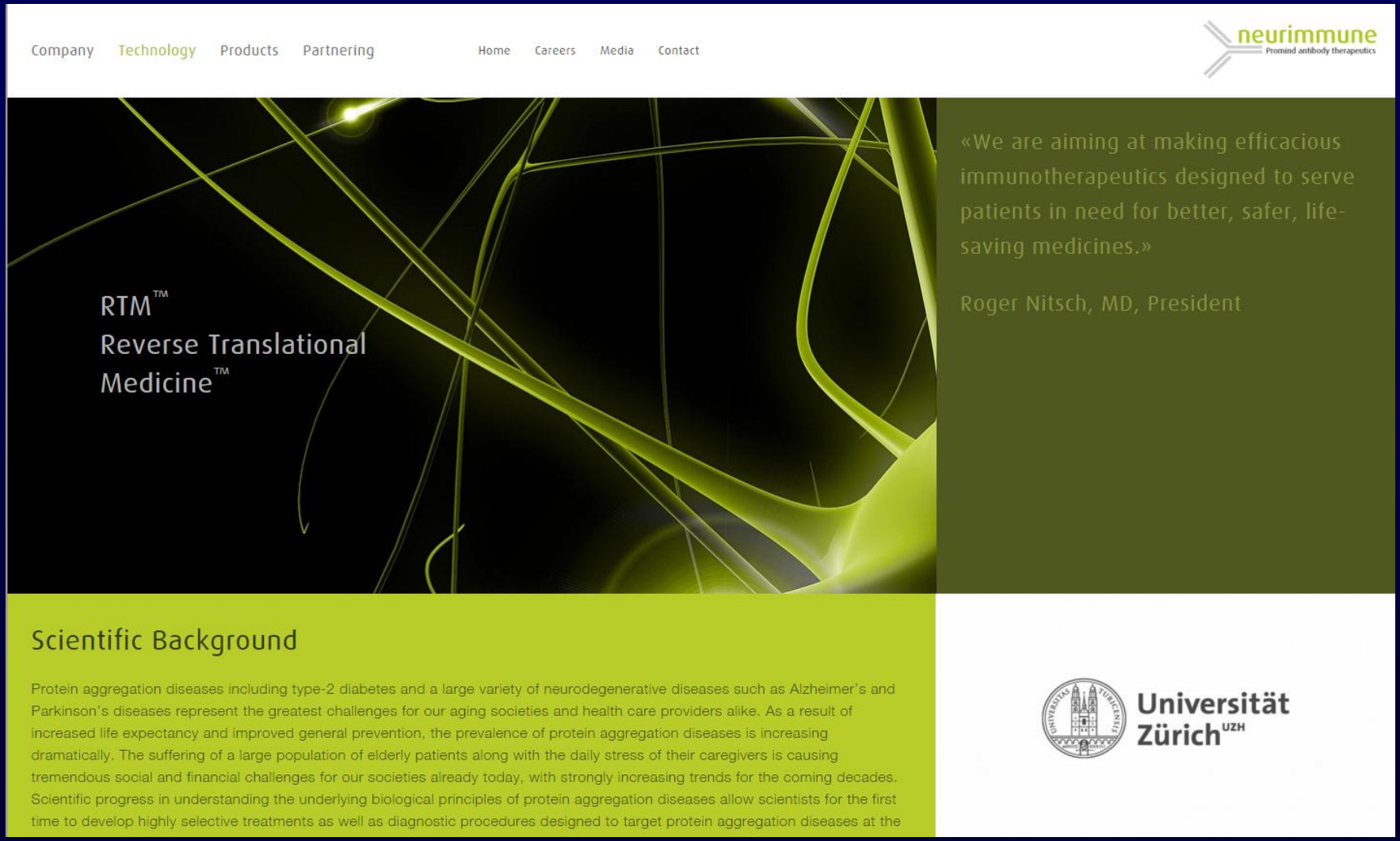
doi:10.1038/nature19323

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

Alzheimer's disease (AD) is characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against Aβ to trigger its clearance or mitigate its neurotoxicity has so far been unsuccessful. Here we report the generation of aducanumab, a human monoclonal antibody that selectively targets aggregated Aβ. In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes and Mini Mental State Examination scores. The main safety and tolerability findings are amyloid-related imaging abnormalities. These results justify further development of aducanumab for the treatment of AD. Should the slowing of clinical decline be confirmed in ongoing phase 3 clinical trials, it would provide compelling support for the amyloid hypothesis.

„humánní protilátky“



Redukce amyloidových plak

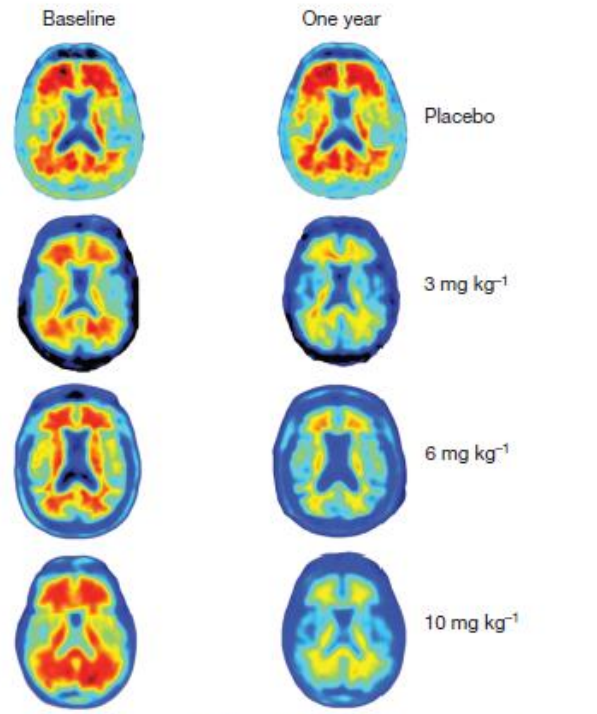


Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54. Individuals were chosen based on visual impression and SUVR change relative to average one-year response for each treatment group ($n = 40$, 32, 30 and 32, respectively). Axial slice shows anatomical regions in posterior brain putatively related to AD pathology. SUVR, standard uptake value ratio.

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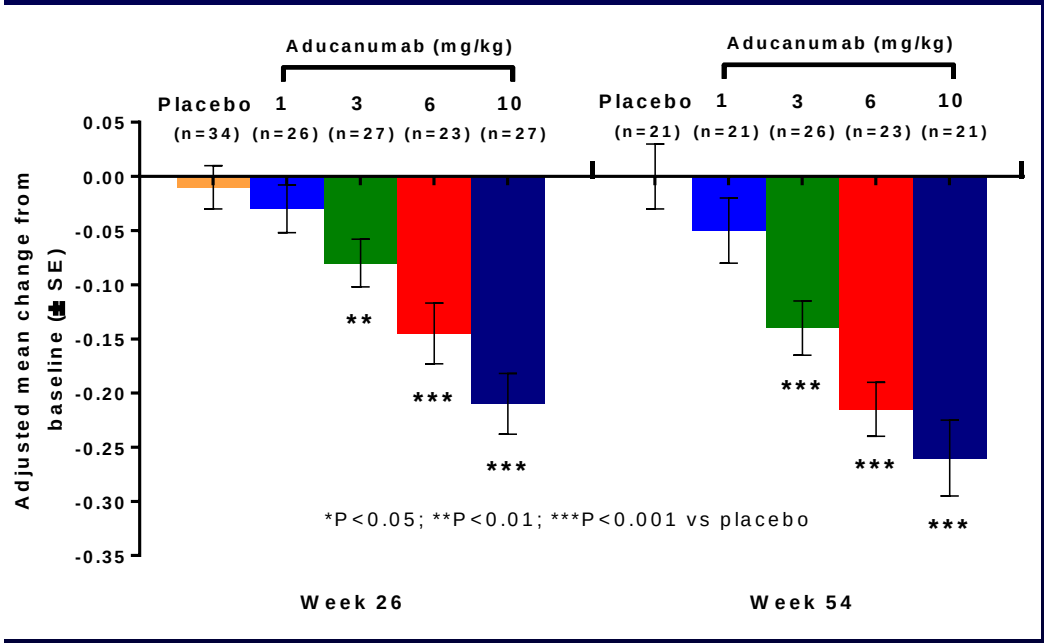
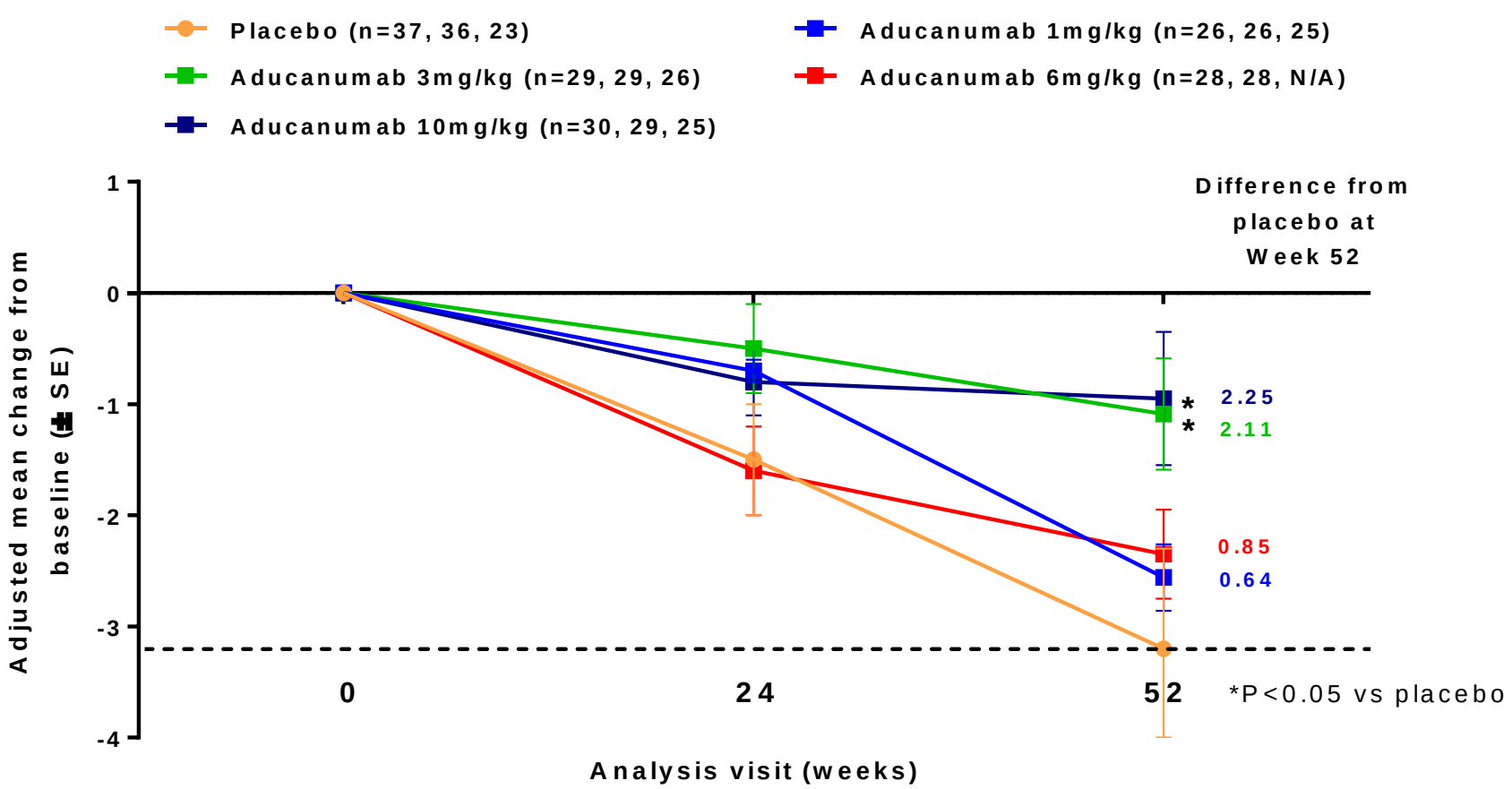


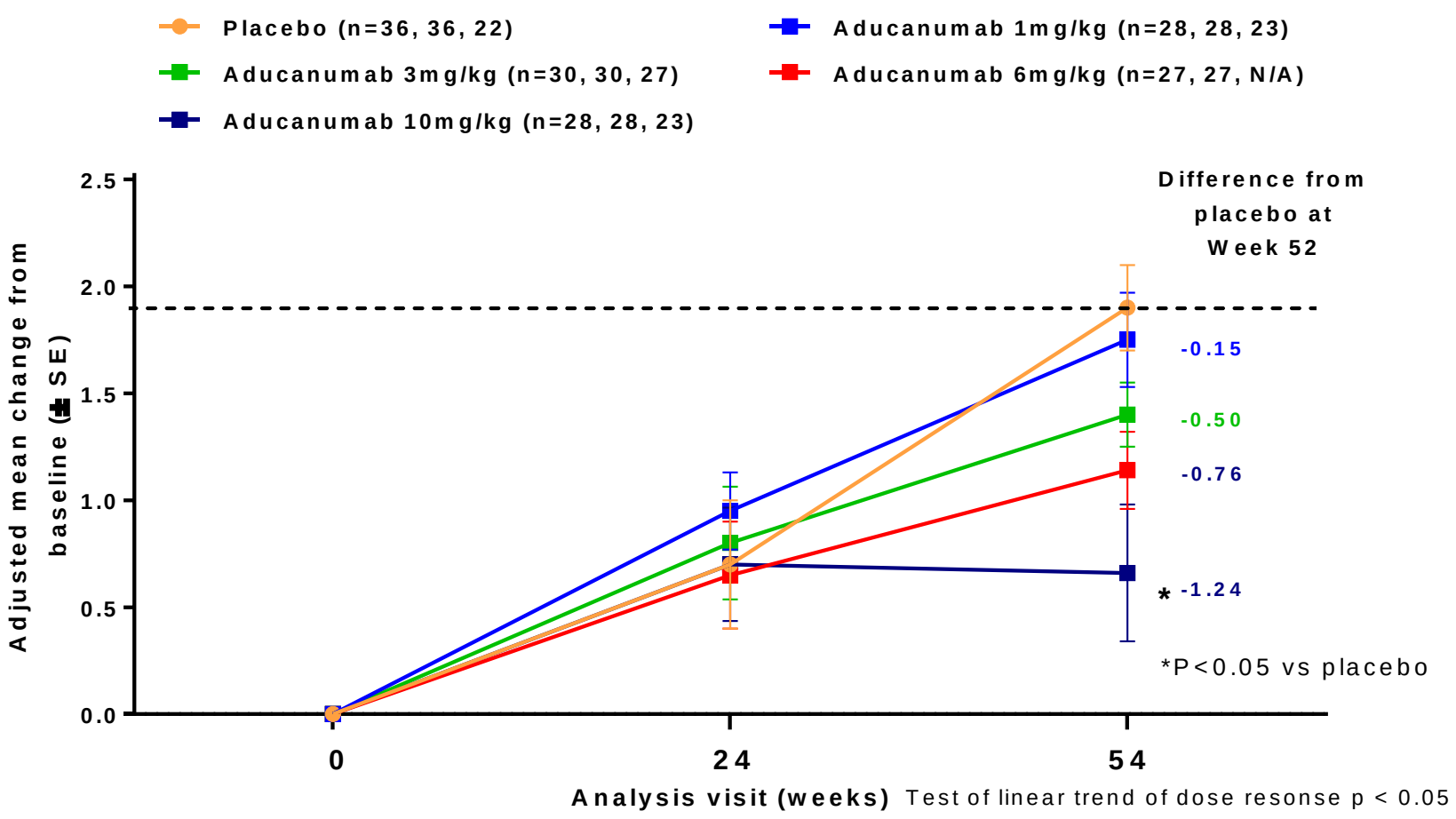
Sevigny et al., 2016

Aducanumab – zlepšení MMSE



Sevigny et al., 2016

Aducanumab zlepšení CDR - sb



Sevigny et al., 2016

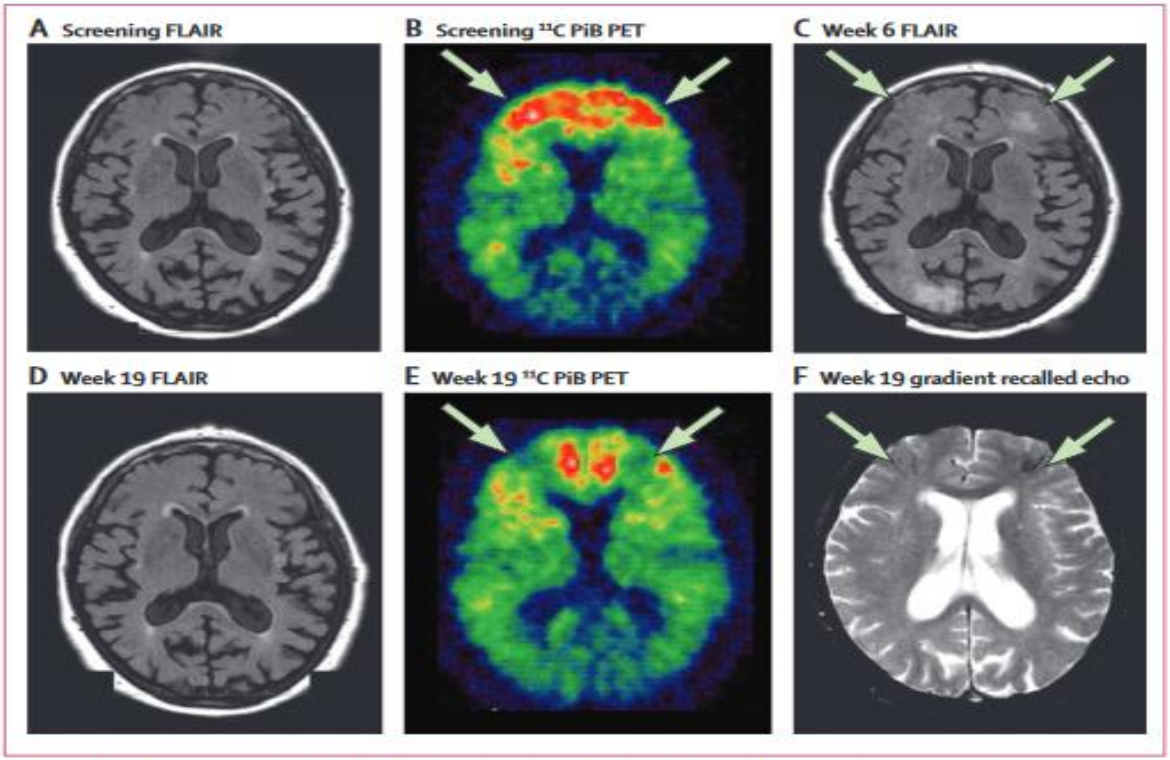
Mohli jsme očekávat lepší výsledky?

- Optimismus Aducanumab:
  - efekt na kognici, soběstačnost a biomarkery (amyloid)
  - závislost na dávce
  - závislost na čase
- Rizika: ARIA (vasogenní edém u vyšších dávek), infuse

	Placebo (n=40)	1 mg/kg (n=31)	3 mg/kg (n=32)	6 mg/kg (n=30)	10 mg/kg (n=32)
Subjects with at least 1 MRI	38	31	32	30	32
ARIA-E n (%)	0/38	1/31 (3)	2/32 (6)	11/30 (37)	13/32 (41)
ApoE ε4 carrier	0/24	1/19 (5)	1/21 (5)	9/21 (43)	11/20 (55)
ApoE ε4 non-carrier	0/14	0/12	1/11 (9)	2/9 (22)	2/12 (17)
Isolated ARIA-H, n (%)	2/38 (5)	2/31 (6)	3/32 (9)	0/30	2/32 (6)

Další zklamání jako bapineuzumab?

- 36% E4 negat. nemělo amyloid na PET, odvozeno od zdravých lidí



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Sperling et al., 2012

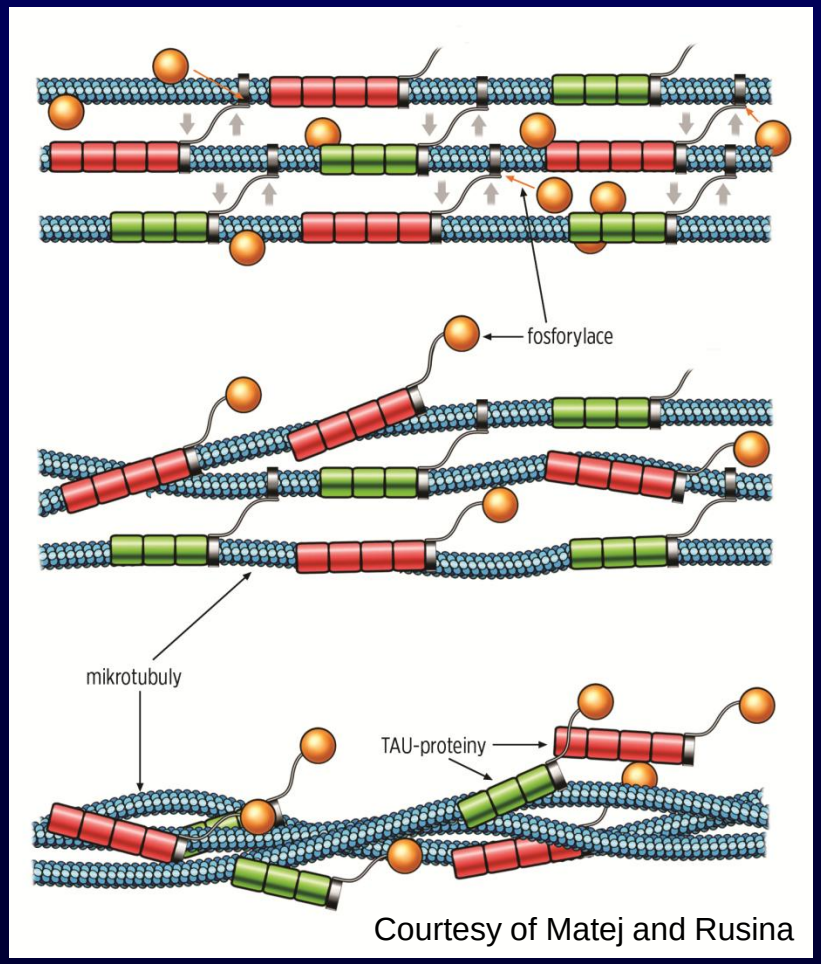
Šance pro ApoE4/E4

- Tamiprosat
  - inhibitor polymerizace Aβ
  - výborná snášenlivost u1500 pacientů (žádné ARIA)
  - účinnost (kognice a soběstačnost) u 1100 ApoE4+

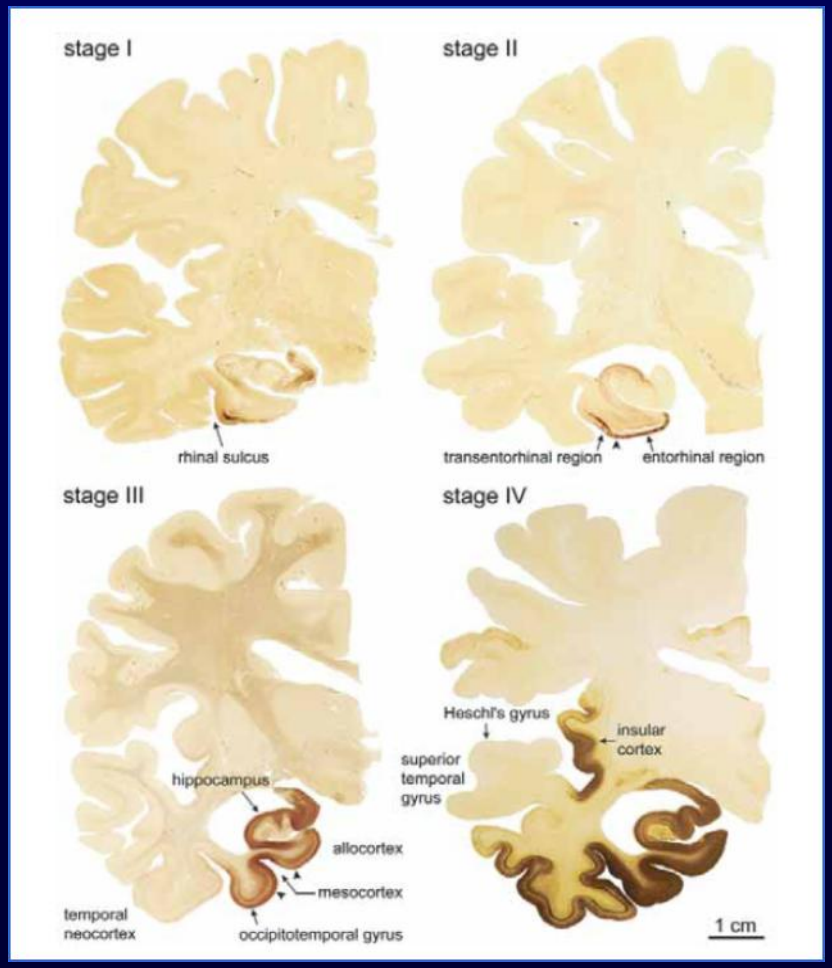
- Prodrug ALZ-801
  - fáze III pouze u populace ApoE4/E4
  - 1x denně

Abushakra et al., Athens/Springfield 2016

2) Příběh Tau

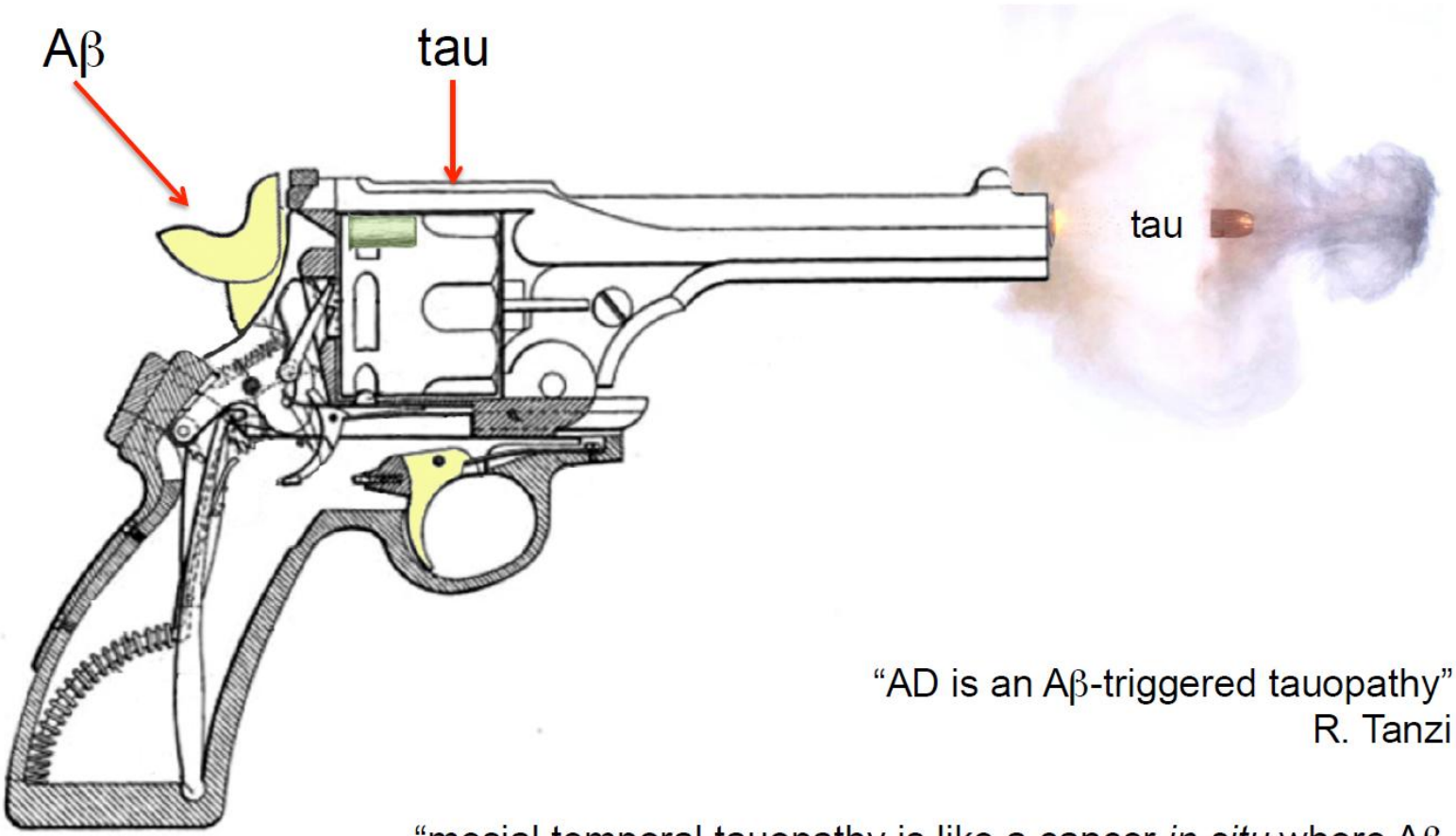


Strukturální protein



Koreluje s klinikou

Relationship between tau and Aβ



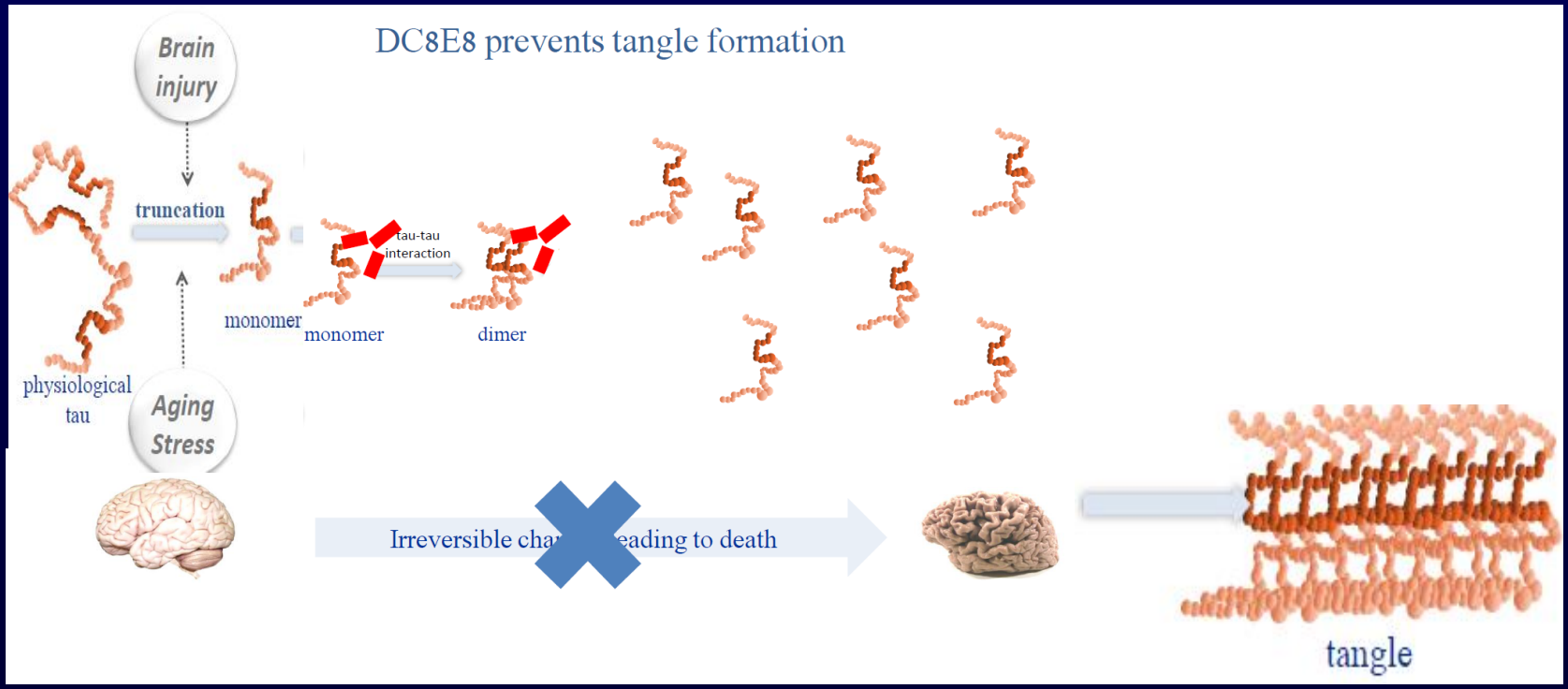
"AD is an Aβ-triggered tauopathy"
R. Tanzi

"mesial temporal tauopathy is like a cancer *in situ* where Aβ, or some other factor, triggers the spread of tau into the rest of the cortex"
J Trojanowski

Strategie léčby tauopathií

Aktivní imunizace	Pasivní imunizace	Inhibitory Tau agregace
• Axon (fáze II) • AC Immune/Janssen	• AbbVie/ C2N • Bristol-Myers Squibb	• TauRx (fáze III) – methylen modř NE
Alzheimerova choroba	Progresivní supranukleární obrna	Alzheimerova choroba, FTLD (malarie)

Zastavení patologické kaskády Tau



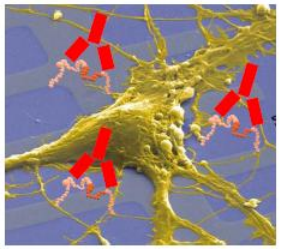
Novak and Zilka 2016

Mechanismus účinku

The main targets of DC8E8 antibody

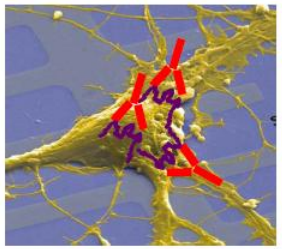
Extracellular pathological tau protein – the main inducer of:

- neuroinflammation
- neurotoxicity



Intracellular pathological tau protein - the major cause behind:

- neurodegeneration
- synaptic dysfunction
- oxidative stress



Novak and Zilka 2016

3) ACH – diabetes 3. typu?

- Zvýšené riziko ACH u diabetiků o 50-100%, ženy

- ACH - větší výskyt diabetu a elevace glykemie (až 81%)

Biessels et al., 2006, Kopf a Folich, 2009, Janson et al., 2004, Yang a Song, 2013

3) ACH – diabetes 3. typu?

- Azeliragon – inhibitor RAGE (povrchový receptor IG sf)
  - RAGE váže Aβo + advanced glycation endproducts (AGE)
  (lipidy a proteiny podléhající glykaci při expozici cukrům)
  - AGEs se tvoří během stárnutí a u diabetu

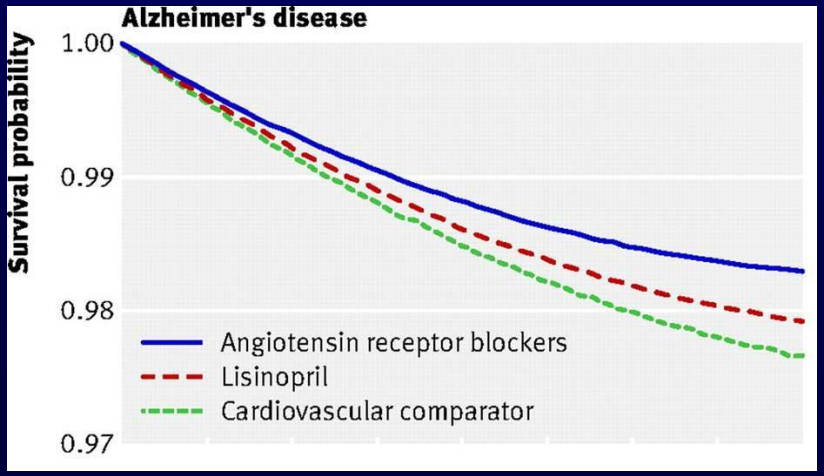
- Insulin - retardovaný - nasálně – studie MCI a mírná ACH

- Pioglitazon – schválen u diabetu
  - insulin sensitizer of the PPAR receptor agonists
  - aktivace PPAR moduluje odpověď na ukládání Aβ
  - 5800 zdravých, 5 let, + predikce MCI-AD u TOMM, ApoE

Claxton et al., 2015, Lyketsos et al., 2012

4) Hypertenze – rizikový faktor ACH

- Není dosud jasné která třída antihypertenziv je lepší
- Preventivní efekt u 816 tis veteránů, 4 roky



- Nilvadipine – blokátor kalciových kanálů

  - bezpečnost dokumentována od roku 1990

  - 8 mg, 18 měsíců, EU, 500 pacientů mírná/střední ACH

Li NC et al. (2010) BMJ 340, b5465

5) Další postupy

- Masitinib - inhibitor protein kinázy c-kit – exprese u rakoviny
  - interference s aktivitou mast cells (zánět, neurodegenerace)
  - 396 pts Madrid, add on mírná/střední ACH (+ fáze II ALS)

- ALZT-OP1 – kombinace 2 FDA schválených léků:
  - stabilizátor mast cell kromolyn (inhalečně) a ibuprofen

- Hluboká mozková stimulace (schválená pro PN)
  - zaslepená studie – ovlivnění Papez okruhu u mírné ACH

Claxton et al., 2015, Lyketsos et al., 2012

6) Symptomatické přístupy

5HT6 – blokáda serotonin receptorů

(zvýší se uvolňování Ach, Glu, NA, D)

- PF-05212377 (Pfizer)
  - fáze II, 12 W, add on, ukončeno 2015, nebyla účinnost

- RVT 101 (Axovant, formally GSK)
  - probíhá III, add on k donepezilu, 24W, dobře snášen,
  - déle, časnější stadia, účinnější?, výsledky 2H 2017

- Lu AE58054 Idalopirdine (Lundbeck),
  - fáze II – efekt na kognici a trend v CDR a CGI,
    ad on k donepezilu in MMSE 12-19, dobře snášen
  - fáze III, 3000 pts, mírná/střední ACH, 3 studie, 1H 2017

agonisté α7 acetylcholin. receptorů

- Selektivní α7 agonista zlepšoval paměť u zvířat:
  SSR180711, MEM3454, encenicline (EVP-6124)

- Fáze II pozitivní výsledky u ACH (EVP-6124 Forum/AbbVie)

- Vzácné ale závažné SAE ve fázi III s EVP – 6124
  - zácpa, ileus
  - **FDA zastavila**

Cena versus výkon

- Vortioxetin - effect size větší než donepezil
- EGb 761

Harrison et al., 2016

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Research Article

RESEARCH ARTICLE

Which Cognitive Domains are Improved by Treatment with Vortioxetine?

John E Harrison, PhD; Søren Lophaven, PhD; Christina K Olsen, PhD

Metis Cognition Ltd., Kilmington Common, UK (Dr Harrison); Alzheimer's Center, VU University Medical Center, Amsterdam (Dr Harrison); H. Lundbeck A/S, Copenhagen, Denmark (Drs Lophaven and Olsen)

Correspondence: John E Harrison, Park House, Kilmington Common, Wiltshire, BA12 6QY, UK (johncpc@btinternet.com)

Abstract

Background: These post hoc analyses evaluated vortioxetine efficacy on cognitive dysfunction in depression. Data were from a double-blind, randomized, fixed-dose, placebo-controlled, 8-week depression study in adults aged 18–65 years (n = 602) with DSM-IV–defined major depressive disorder (MDD). Subjects were randomized (1:1:1) to vortioxetine 10 mg/day or 20 mg/day or placebo.
Methods: Cognitive function was assessed at baseline, Week 1 (10 mg/day only) and Week 8 using Digit Symbol Substitution Test (DSST) number of correct symbols, Rey Auditory Verbal Learning Test, Trail Making Test, Stroop test, Simple Reaction Time, and Choice Reaction Time tests. The cognition variables were standardized and used for constructing composite Z-scores for the cognitive domains of executive function, attention/speed of processing, and memory.
Results: At Week 1, vortioxetine 10 mg/day separated from placebo for attention/speed of processing (standardized composite Z-score = 0.21; $p = 0.0238$) and DSST number of correct symbols (standardized effect size = 0.18; $p = 0.0458$) and for executive function (standardized composite Z-score = 0.20; $p = 0.0274$). At Week 8, vortioxetine 10 mg/day and 20 mg/day separated from placebo for executive function and attention/speed of processing, with standardized composite Z-scores ranging from 0.35 to 0.49 (all $p < 0.01$). Standardized composite Z-scores for memory were 0.31 ($p = 0.0036$, 10 mg/day) and 0.22 ($p = 0.0349$, 20 mg/day). Standardized effect sizes for DSST were 0.51 ($p < 0.0001$, 10 mg/day) and 0.52 ($p < 0.0001$, 20 mg/day). Results are limited by the post hoc nature of the analyses and the absence of an active reference in the original study.
Conclusions: Vortioxetine (10 and 20 mg/day) had a multi-domain beneficial effect on cognitive performance, as evidenced by improvements in measures of executive function, attention/speed of processing, and memory. The effect on the DSST may be due to improvements in several cognitive skills.

Keywords: cognitive domains, composite Z-score, depression, vortioxetine

ApoE a cholesterol

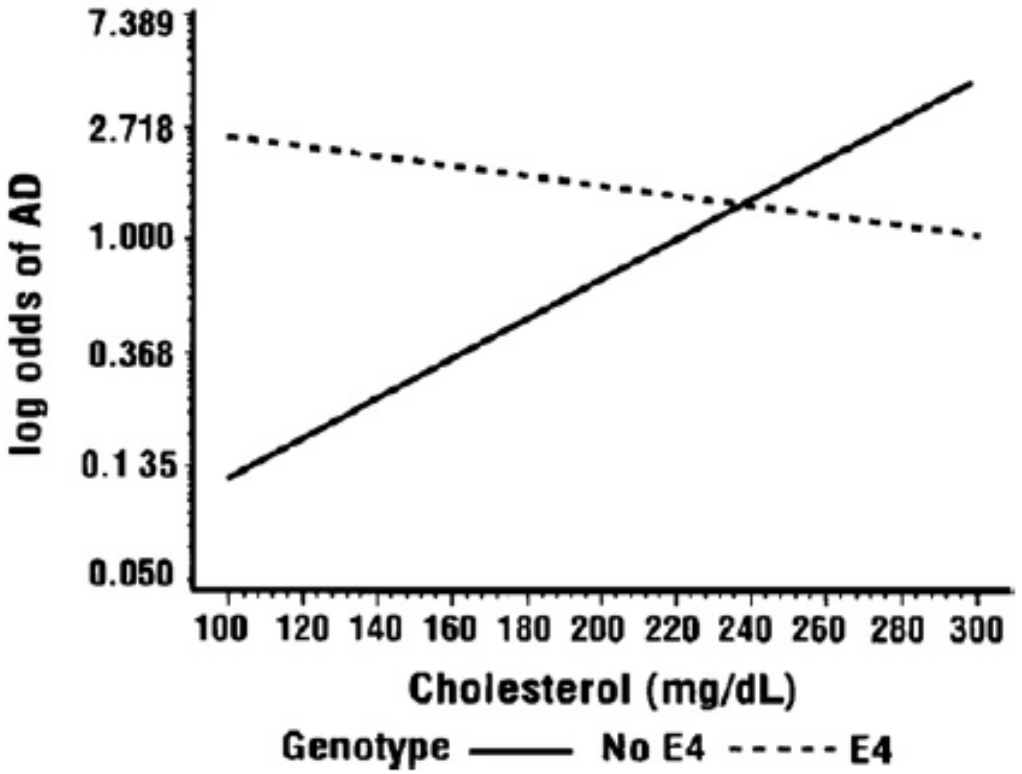

Fig. 1. Log odds of AD vs. cholesterol level (mg/dL) by e4 status. From Evans et al. (2000) with permission.

Cukry

Studie: cukrovarníci platili vědce, aby ze srdečních chorob vinili tuk

14. září 2016 8:31

Potravinářský průmysl se snažil víc než půlstoletí penězi ovlivňovat vědu o výživě a zdravotnictví, tvrdí nová studie kalifornských výzkumníků. Vědci z Harvardu podle ní zkreslili fakt, že konzumace cukru má nějaký vliv na kardiovaskulární nemoci.

ACH – strategie léčby