Herinneringen
(Memories)

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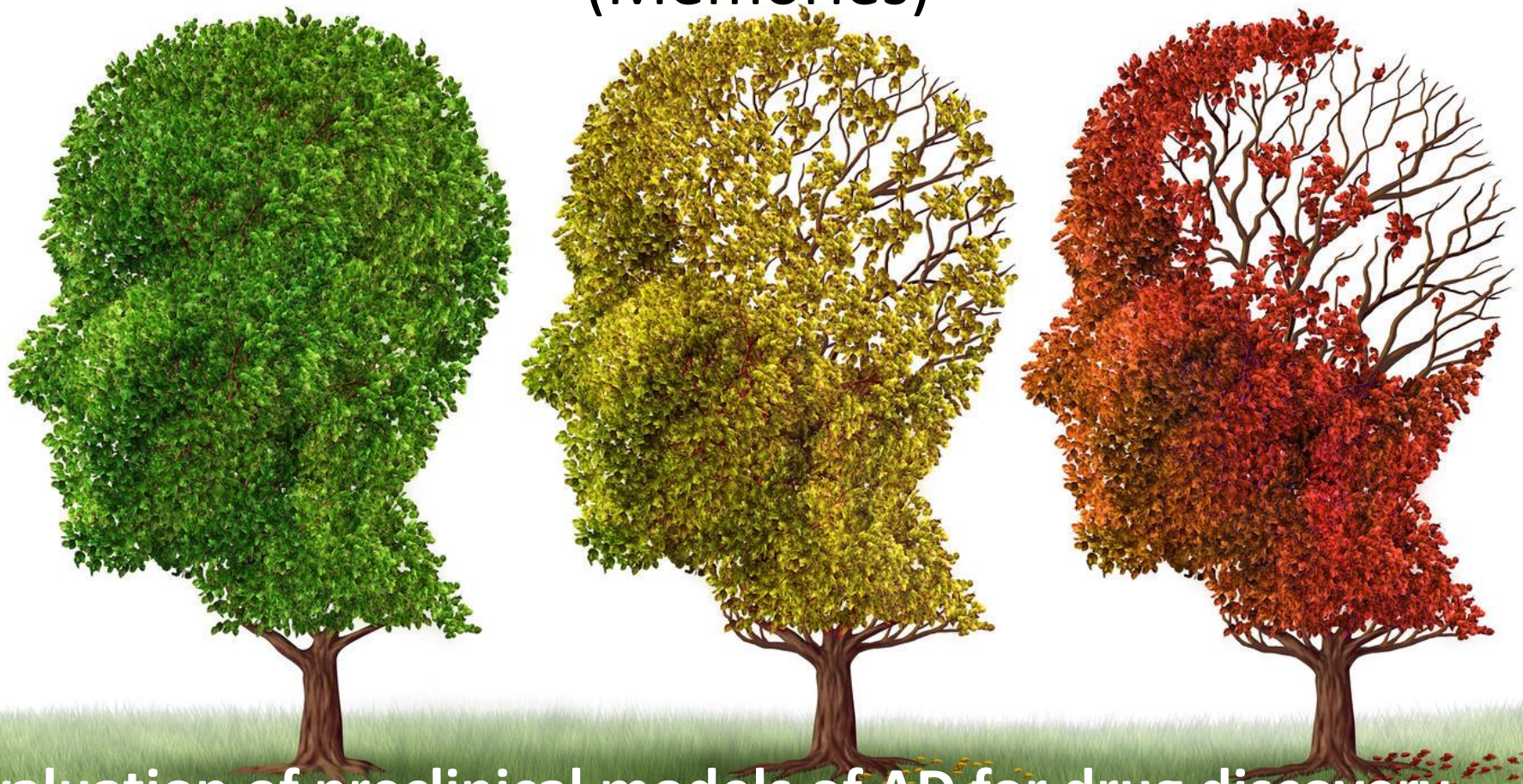

Evaluation of preclinical models of AD for drug discovery

Gerard Griffioen, reMYND

23/11/2018

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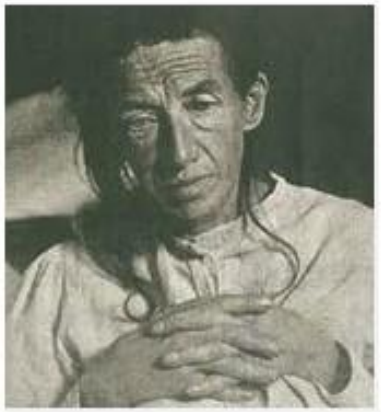
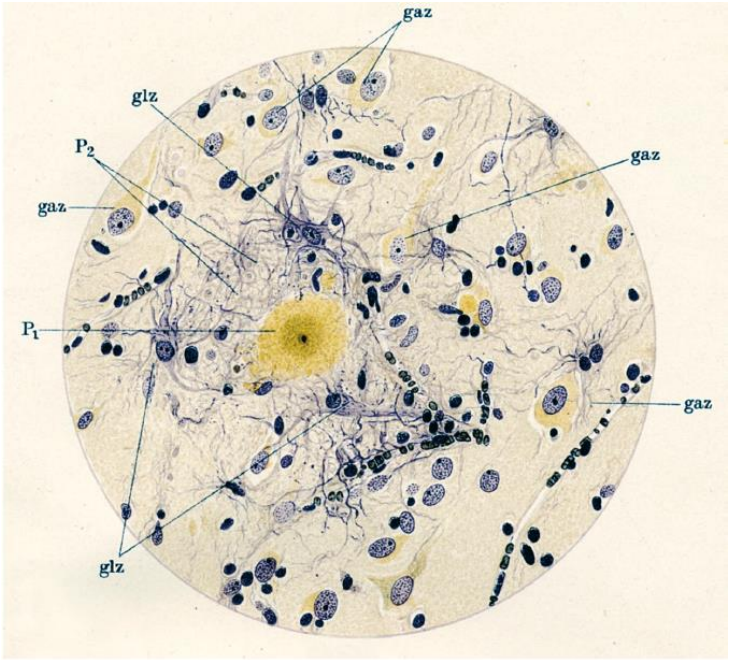
Plaques and tangles are pathological hallmarks of Alzheimer's disease

Alois Alzheimer



Auguste D.
1st described case*



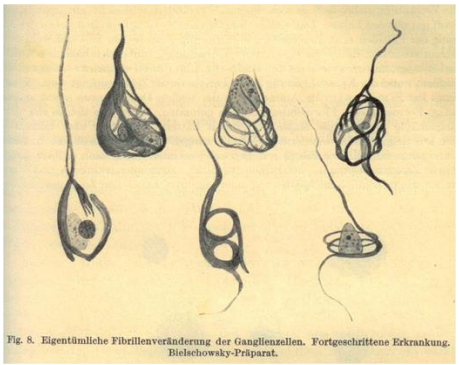


Fig. 8. Eigentümliche Fibrillenveränderung der Ganglienzellen. Fortgeschrittene Erkrankung. Bielschowsky-Präparat.

"In the centre of an otherwise almost normal cell there stands out one or several fibrils due to their characteristic thickness and peculiar impregnability".
Alzheimer's description of tau neurofibrillary tangles

"Numerous small miliary foci are found in the superior layers. They are determined by the storage of a peculiar material in the cortex"
Alzheimer's description of amyloid-beta plaques

*Alzheimer A. Über einen eigenartigen schweren ErkrankungsprozeB der Hirnrinde. Neurologisches Centralblatt 1906; 23: 1129–36. Allgemeine Zeitschrift fur Psychiatrie und Psychisch-gerichtliche Medizin. 1907; 64: 146–48.
Alzheimer, A. (1911) Über eigenartige Krankheitsfälle des späteren Alters. Zeitschrift für die Gesamte Neurologie und Psychiatrie 4, 356–385

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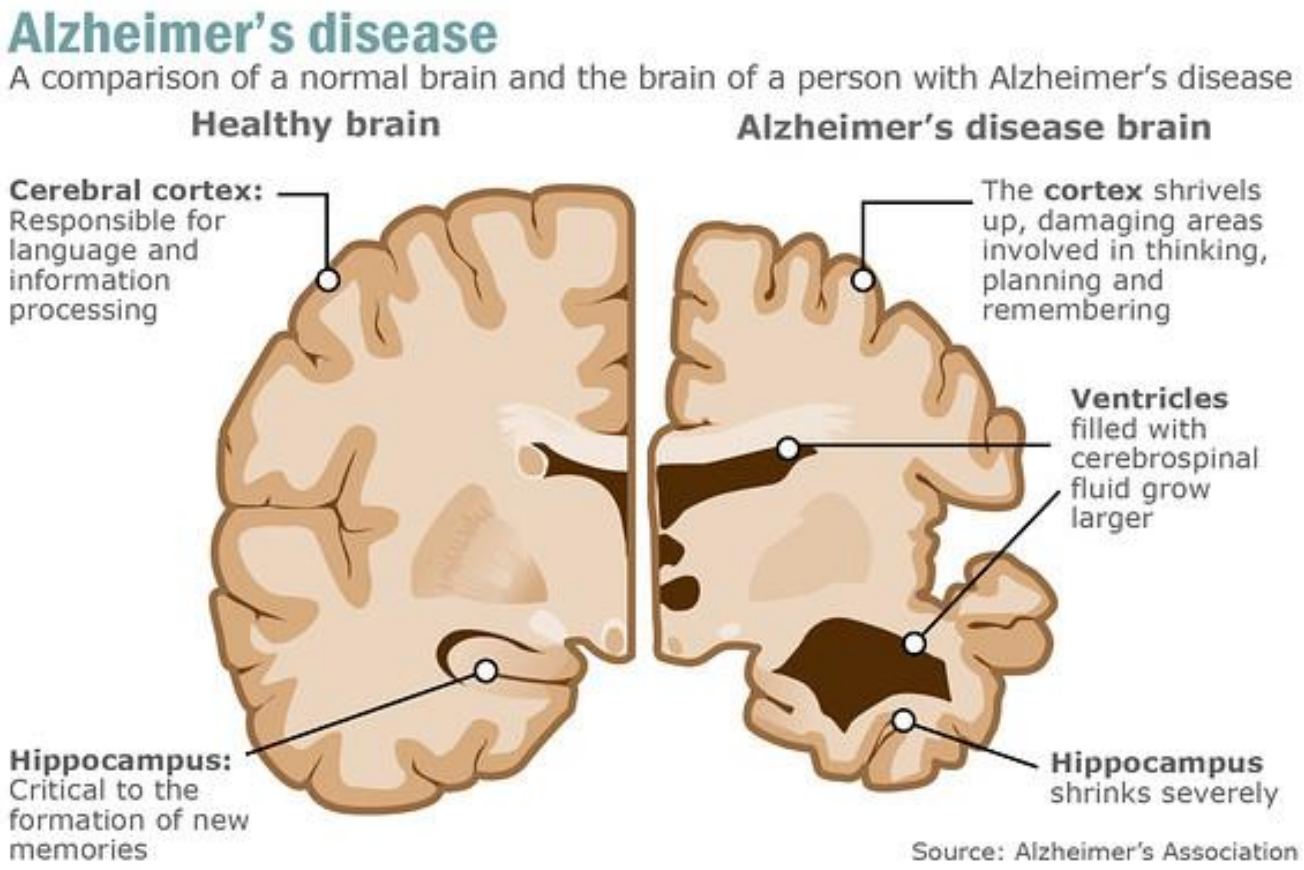
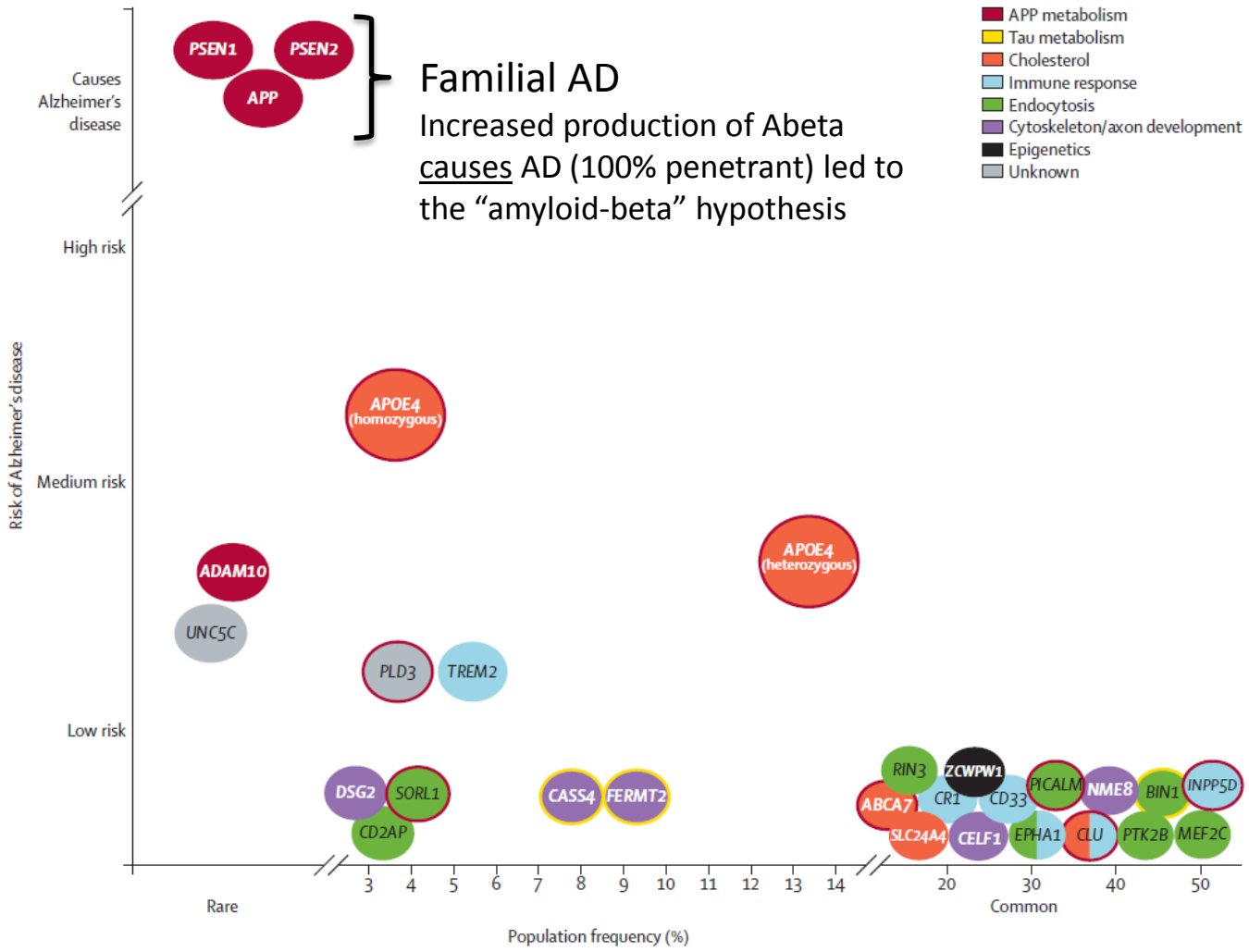
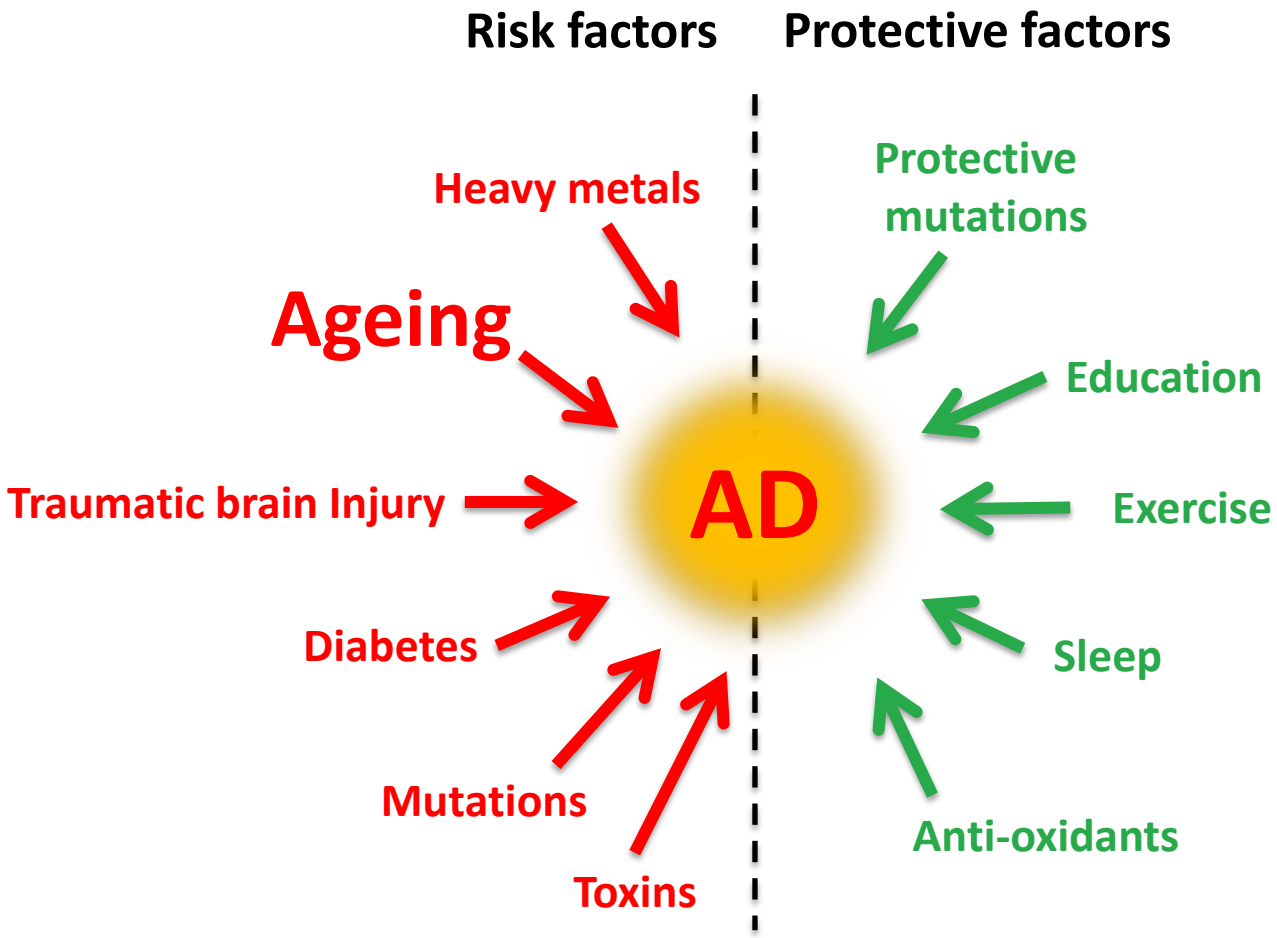
Neuronal loss results in a dysfunctional brain which underlies Alzheimer's disease symptoms



Genetic risk factors of Alzheimer's disease



Non-genetic risk factors and protective factors of Alzheimer's disease



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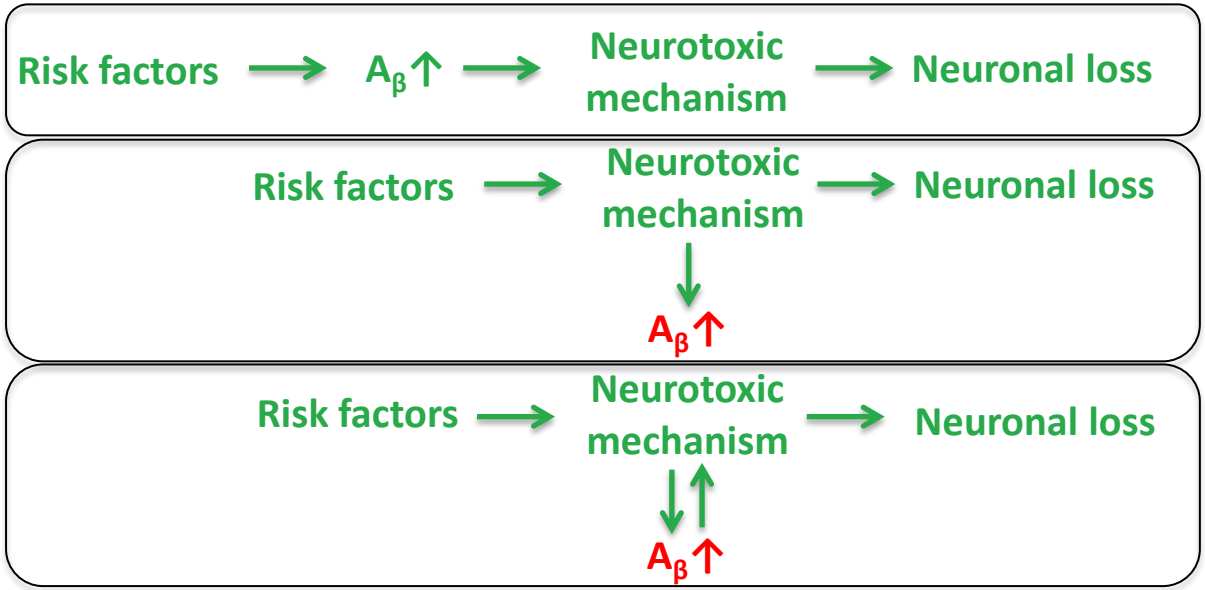
AD: not one cause but many, but what neurotoxic mechanism do they have in common?

Familial AD (<5%)

Autosomal dominant mutations which increase the self-polymerization of Abeta

Sporadic AD (>95%)

A unique constellation of genetic and/or non-genetic AD risk-factors, either positive or negative, determines the onset and progression of Alzheimer's disease in a given patient



"Amyloid-beta" hypothesis

"Tomb stone" hypothesis
(fAD is phenocopy…)

"Mixed" hypothesis
(Abeta as accelerator)

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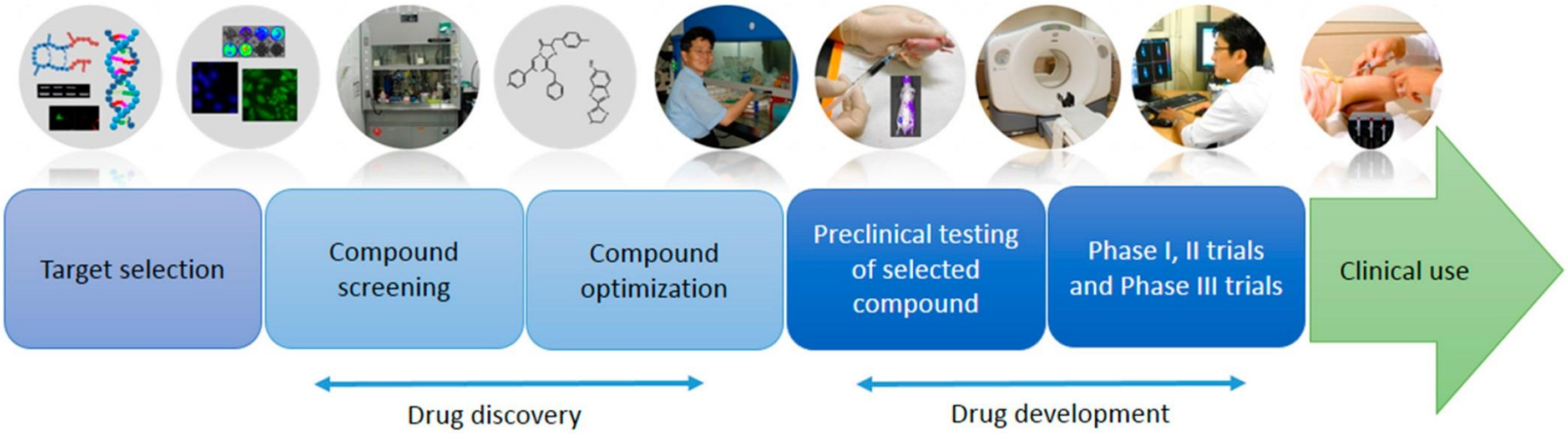
The drug discovery process

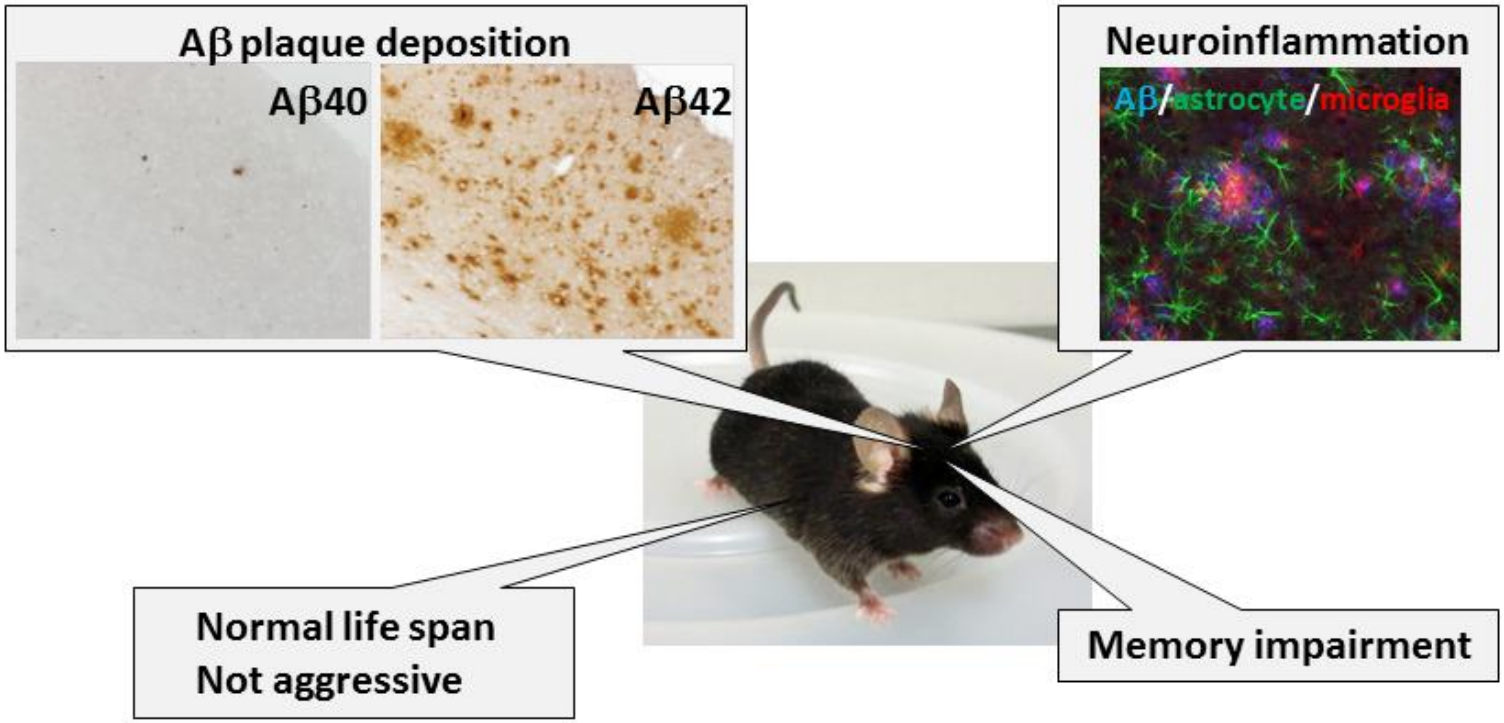


Which mechanism drives the disease?

Which compound modifies the mechanism best in-vitro?

Is the compound working in animal models and subsequently in patients by modifying the mechanism?

Transgenic APP mice, a heavily used model for AD drug discovery, models familial AD



- (Over)-expression of human APP with familial mutation: increased Abeta drives the neurotoxic mechanism
- Cognitive dysfunction
- No tau pathology or obvious neuronal cell loss
- Excellent model to evaluate treatments targeting Abeta, but how relevant is this for sporadic AD?

Interreg: mouse model of sporadic AD to recapitulate sporadic AD better (WP4.1)

AD risk factors singly and combined

- Ageing
- Fipronil
- Copper
- Mutations APP
- ….

AD pathology and symptoms?

Blood/CSF miRNA profile altered as in patients?

If successful the model would facilitate sporadic AD research and drug discovery

- ➢ Studying the underlying mechanisms of neurotoxicity triggered by risk factors
- ➢ Development of biomarkers for diagnosis and treatment effects
- ➢ Assessing potential risk factors of AD
- ➢ Efficacy testing of AD treatments (=one of reMYND's core businesses)

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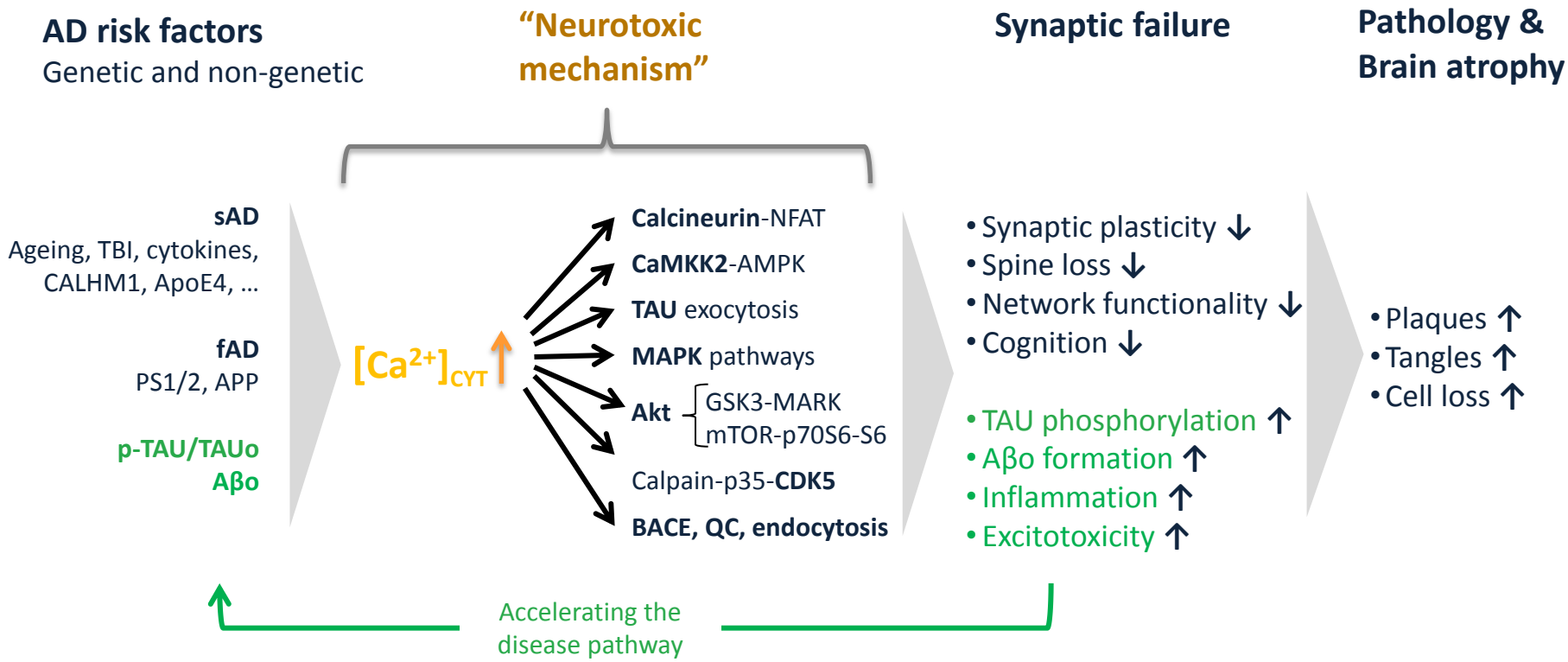
Ca^{2+} dyshomeostasis is central in the disease pathway ("neurotoxic mechanism") of familial AD and sporadic AD

Simplified working model ("mixed" hypothesis) as to how genetic and non-genetic AD risk-factors converge into a common disease pathway



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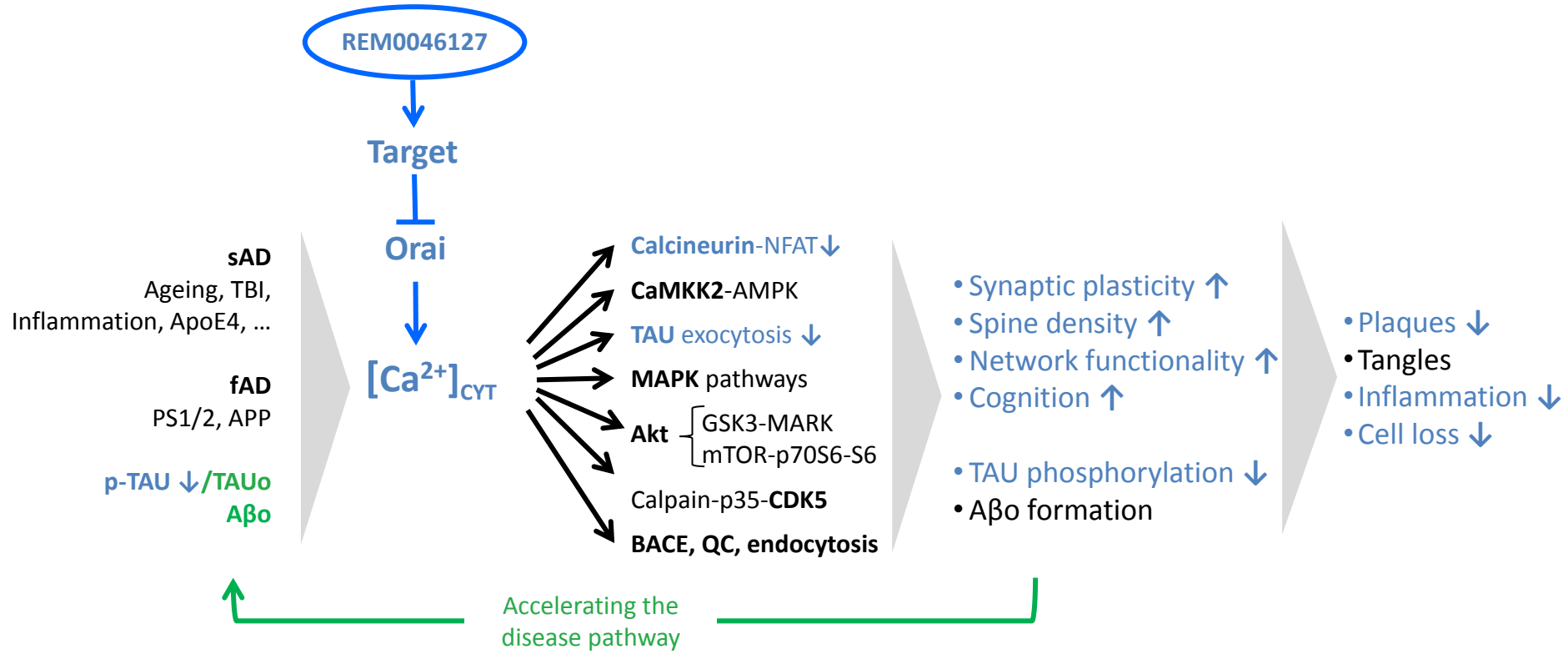
Restraining Orai mediated Ca^{2+} influx prevents setting-off the AD cascade in different preclinical models



In **blue** effects REM0046127 demonstrated so far: fast symptomatic effects and disease-modification

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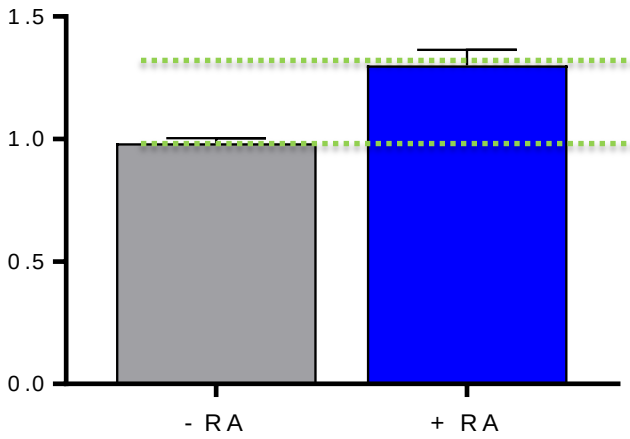
ReS19-T reduces elevated cytosolic calcium in pathological conditions towards physiological levels but not below

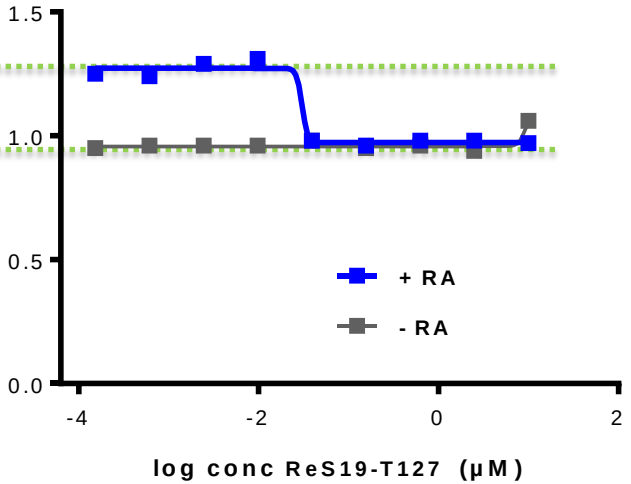
Tau cell-based assay of calcium dyshomeostasis and toxicity

Cytosolic Calcium
Fura-2 ratio 340:380nm (mean ± SEM)



The inducer increases basal calcium levels, in the absence of treatment

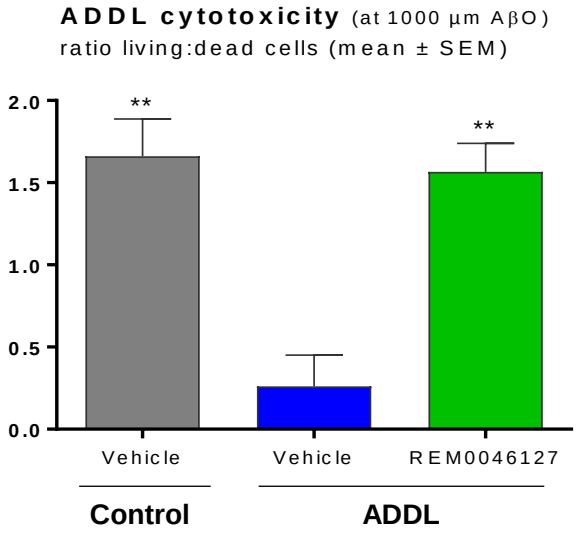
Cytosolic Calcium
Fura-2 ratio 340:380nm (mean ± SEM)

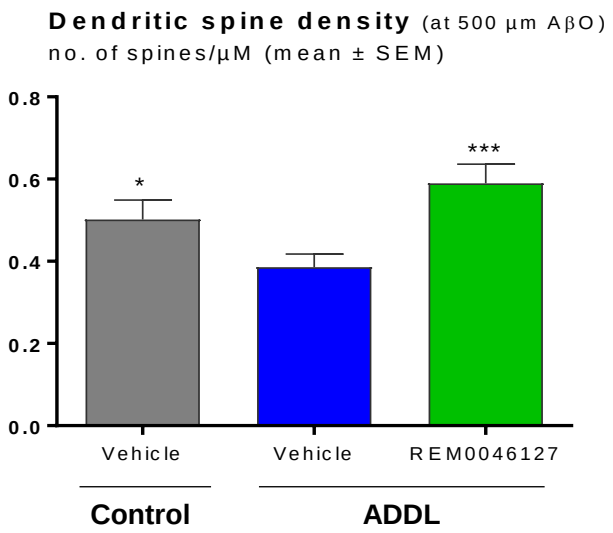


ReS19-T reduces pathological calcium levels to physiological levels, but not below, even at more than 1.000 times the EC50

REM0046127 blocks Aβ oligomers (ADDL) mediated neurotoxicity

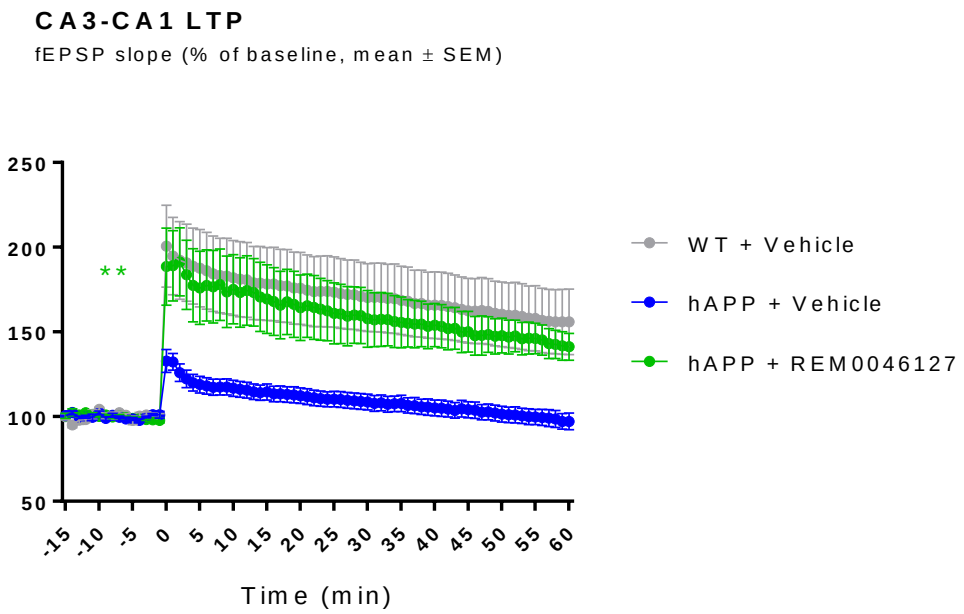
Primary hippocampal cell culture rat, Aβo incubation, 24 hr





REM0046127 restores LTP in hAPP mice after 7 days treatment...

LTP in CA3-CA1 (L-LTP), hAPP mice, 7 months, n = 5-6, 7 days treatment, PO, qd, REM0046127, 20 mg/kg/day



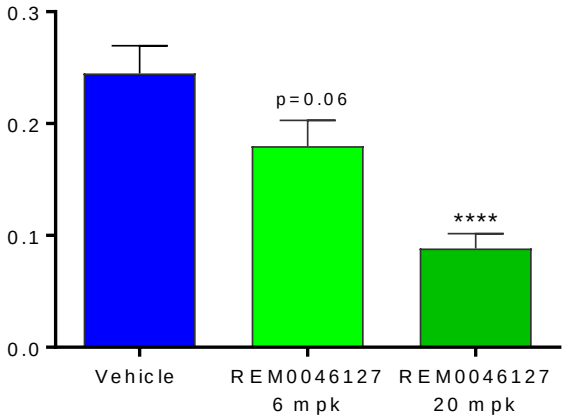
- Also LTP rescue after 7 days of treatment in transgenic hTau mice
- ED50 LTP rescue: 6 mg/kg (=16 nM free compound in brain)

REM0046127 decreases amyloid plaque load and associated inflammation

hAPPxPS1 mice, REM0046127, PO, 3 months treatment

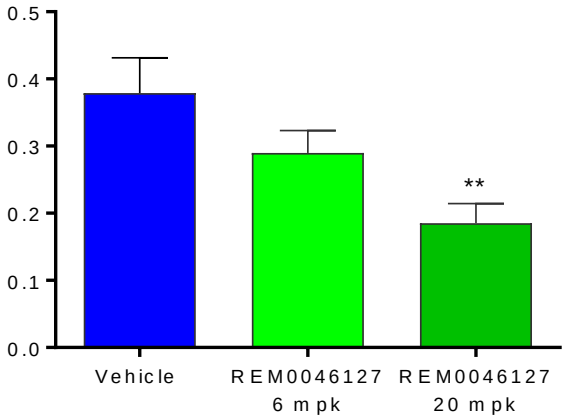
Diffuse amyloid plaque load, cortex after 3 months treatment

Area % (mean ± SEM)



Inflammation, CD11b, cortex after 3 months treatment

Area % (mean ± SEM)



But is REM0046127 also efficacious in sporadic AD?

WP4.2 testing an AD-candidate drug in the to be developed sporadic AD model (WP4.1)

If successful:

- Illustrates that Ca^{2+} dyshomeostasis may be the common key process for both sporadic and familial AD (the underlying neurotox mechanism is the same)
- Confirms REM0046127 is efficacious for sporadic AD population
- The miRNA profile could be used as a biomarker read-out in clinical trials for REM0046127

Co-financiering

Dit project is mede mogelijk gemaakt door co-financiering van:

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Ministerie van Economische Zaken

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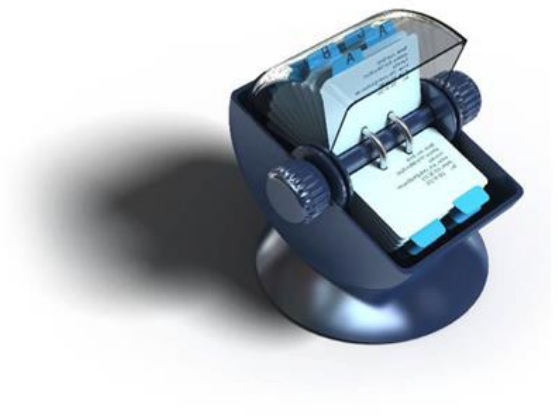
Contact reMYND



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