SELECTED OPPORTUNITIES IN NEUROSCIENCE

Soluble APPsα-based Gene Therapy in Alzheimer's Disease (BIO15161)

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Product factsheet

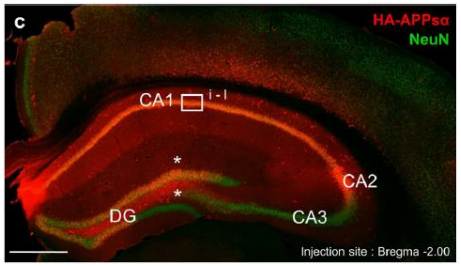
- **Product: Adeno associated virus expressing soluble amyloid precursor protein (APPsα)**
- **Mechanism:**
  - Aβ is generated by sequential cleavage of APP by β- and γ-secretase
  - In the competing non-amyloidogenic pathway, α-secretase cleaves APP precluding the formation of Aβ peptides and leading to the secretion of the neuroprotective ectodomain APPsα
  - AD is characterized by upregulation of β-secretase and a concomitant reduction in APPsα
  - Loss of APPsα physiological functions contribute to AD pathogenesis
  - α-secretase attenuating mutations have been associated with hereditary late-onset AD
- **Phase of development:** in vivo PoC
  - AAV-APPsα injection in the hippocampus of AD mice mediates efficient and long lasting neuronal expression of APPsα
  - APPsα expression rescues spatial memory, synaptic plasticity and neuropathology in AD mice
- **Potential applications:** Alzheimer's disease
- **Patent:** PCT/EP2016/063338 / Priority date 12th June 2015
- **Ref:** "Viral gene transfer of APPsα rescues synaptic failure in an Alzheimer's disease mouse model". *Acta Neuropathol (2016).*

SOLUBLE APPSα-BASED GENE THERAPY IN ALZHEIMER'S DISEASE (BIO15161)

Proof of Concept

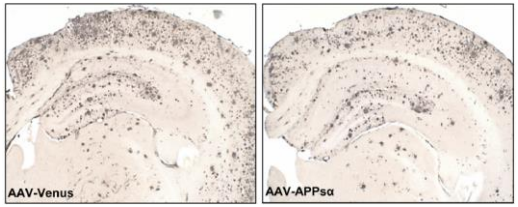
AAV-APPsα treatment reduces neuropathology of AAP/PSIΔE9 mice

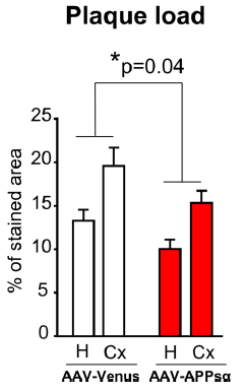
Widespread expression of APPsα in the hippocampus and cortex of injected AD mice



Mice were injected in the hippocampus with an AAV9 expressing APPsα specifically in neurons at 12 months of age and sacrificed 5 months later.

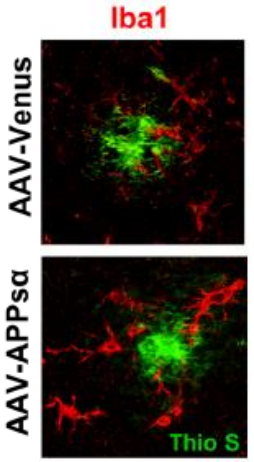
AAV-APPsα injection reduces amyloid plaques in AD mice

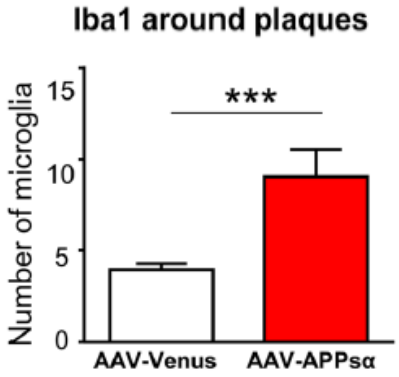




Representative image of cortex and hippocampus of AD mice injected with control or AAV-APPsα vector (left pannel) and quantification of amyloid plaques (right pannel).

AAV-APPsα induces microglia recruitment and activation in the vicinity of amyloid plaques





Microglia was stained with an Iba1 antibody. Left pannel shows a representative image of recruitment and activation of microglial cells around amyloid plaques. Right pannel shows a quantification of microglial cells in the vicinity of amyloid plaques.

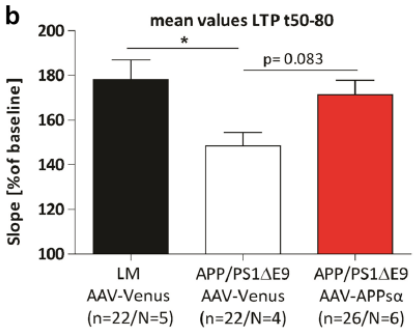
SOLUBLE APPSα-BASED GENE THERAPY IN ALZHEIMER'S DISEASE (BIO15161)

Proof of Concept

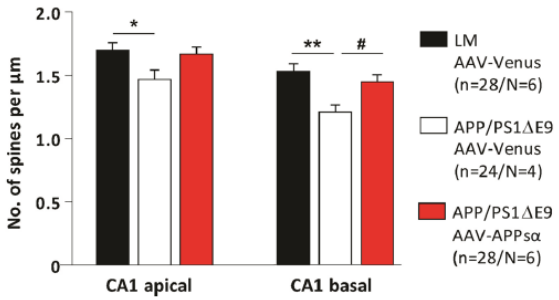
AAV-APPsα treatment reduces synaptic deficits and memory of AAP/PSIΔE9 mice

Effect of AAV-APPsα injection on synaptic deficits

LTP

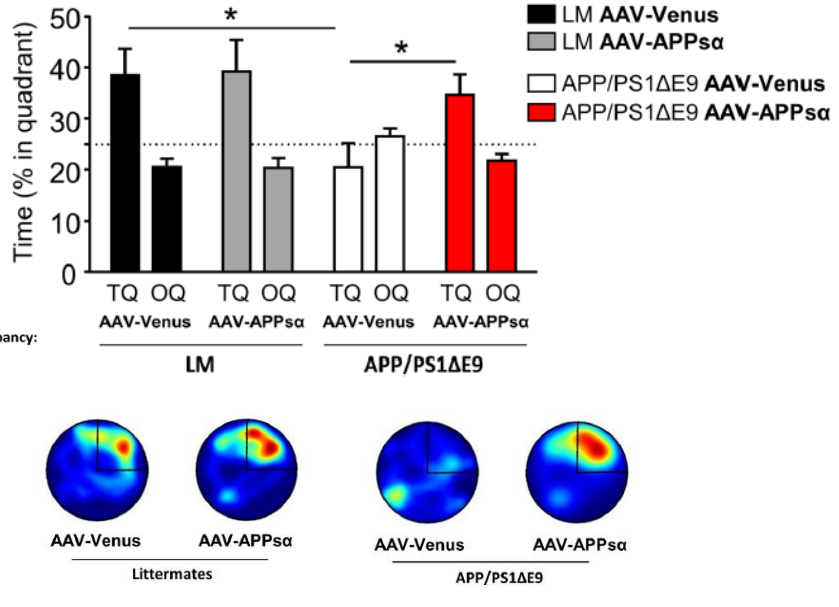


Dendritic spines

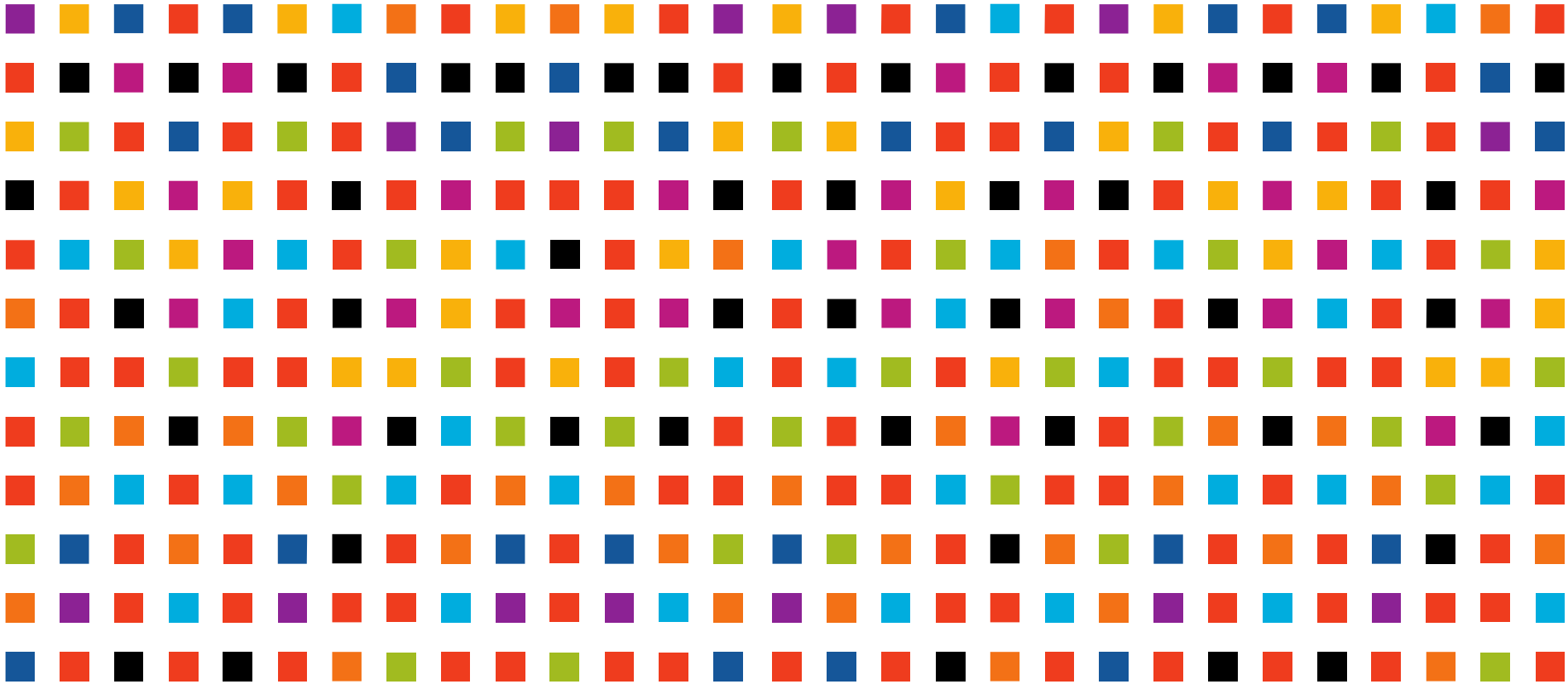


Long-term potentiation (LTP, upper panel) and dendritic spines (lower panel) were improved in transgenic mice injected with AAV-APPsα compared to control (mice injected with AAV-Venus).

Effect of AAV-APPsα injection on spatial memory



WT and Transgenic mice were stereotaxically injected with AAV-APPsα or AAV-Venus at 12 months of age and tested 2 months later in the Morris water-maze place navigation task. AAV-APPsα treatment improves long-term spatial memory.



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