SELECTED OPPORTUNITIES IN NEUROSCIENCES

Pyk2-based gene therapy attenuates cognitive deficits associated to Huntington's disease (HD) (BIO17059)

PYK2-BASED GENE THERAPY ATTENUATES COGNITIVE DEFICITS ASSOCIATED TO HUNTINGTON'S DISEASE (HD) (BIO17059)

Product factsheet

stage

- **Product: Adeno associated virus expressing Pyk2**
- **Mechanism:**
  - Pyk2 is a non-receptor calcium-dependent tyrosine kinase highly expressed in the hippocampus
  - *PTK2B,* the gene encoding Pyk2, is a susceptibility locus for Alzheimer's disease
  - Pyk2 knockout impairs hippocampal-dependent memory and LTP in mouse
  - NMDA receptors and PSD-95 are altered in Pyk2 mutant mice
  - Spines are altered in the hippocampus of Pyk2 mutant mice
  - Pyk2 deficit alters NMDA-induced PSD-95 recruitment in spines
- **Phase of development:** in vivo PoC
  - Pyk2 expression and synaptic markers are altered in Huntington's disease (HD)
  - Restoring Pyk2 expression through hippocampal AAV injection rescues the hippocampal phenotype of HD mice
- **Potential applications:** Huntington's disease (PoC)
- **Patent:** EP17305340 / Priority date 24 March 2017
- **Ref:** « Pyk2 modulates hippocampal excitatory synapses and mediates Huntington's disease (HD) cognitive deficits » Nature Comm, May 2017

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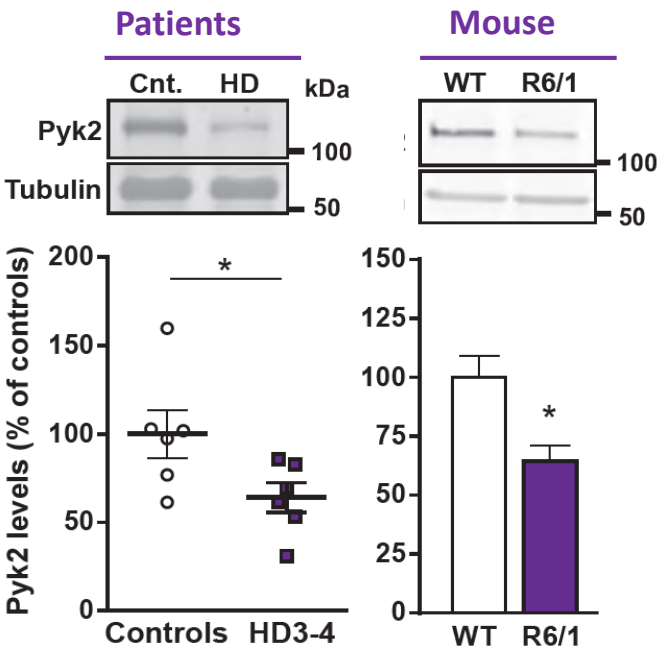
Proof of Concept

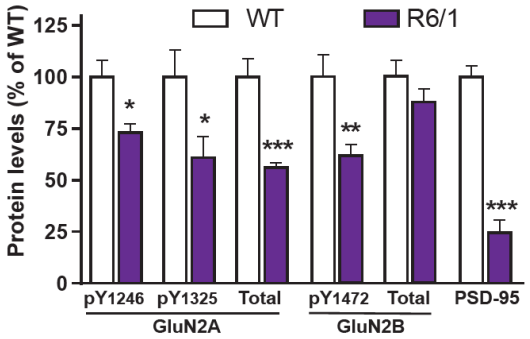
Hippocampal alterations of Pyk2 and synaptic markers in Huntington's disease

Pyk2 expression is altered in HD

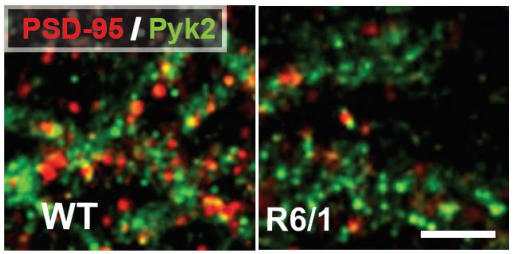


Hippocampal porst-mortem samples from human patients and control and from WT and R6/1 transgenic mice were analyzed by immunoblotting and quantified . Tubulin was used as a loading control.

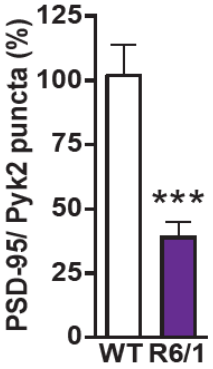
Synaptic markers are altered in HD



Immunoblotting for phosphorylated and total GluN2A and GluN2B, and PSD-95 in hippocampus of WT and R6/1 mice.



Confocal images of the of CA1 hippocampal sections from WT and R6/1 mice immunolabeled for PSD95 (red) and Pyk2

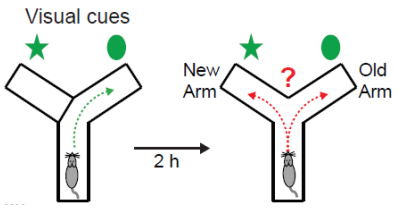


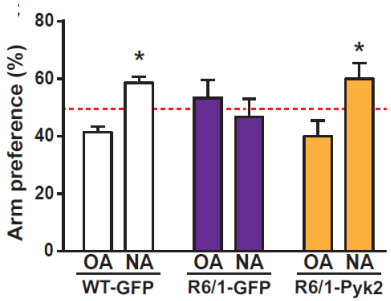
PYK2-BASED GENE THERAPY ATTENUATES COGNITIVE DEFICITS ASSOCIATED TO HUNTINGTON'S DISEASE (HD) (BIO17059)

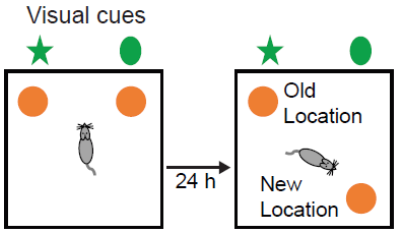
Proof of Concept

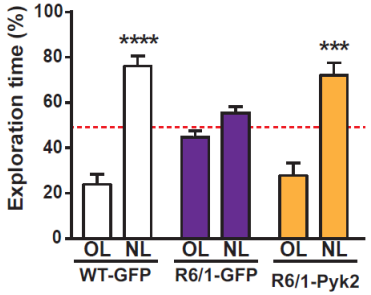
Pyk2 protein levels restoration in the hippocampus rescues R6/1 mouse cognitive phenotype

Pyk2 expression recovery improves hippocampal phenotype of R6/1 mice



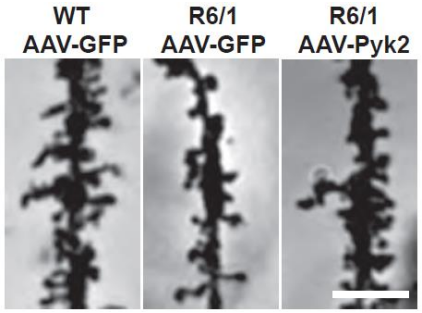


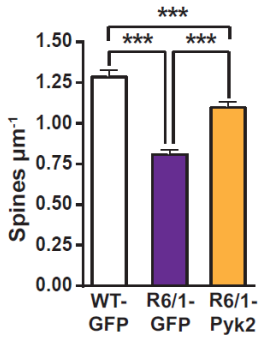




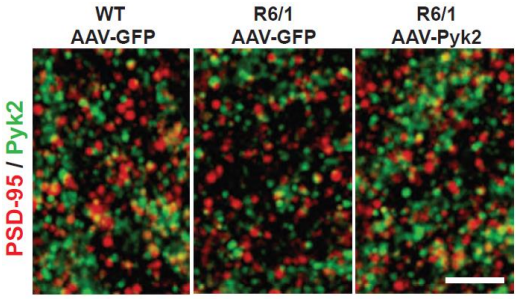
Y-maze and novel object location tests were used to assess cognitive performances of HD mice.

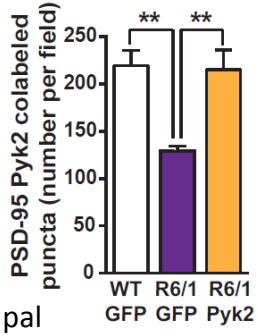
Pyk2 expression recovery improves synaptic abnormalities in R6/1 mice





Golgi-Cox staining of hippocampal dendrites from CA1 pyramidal neurons and quantification.





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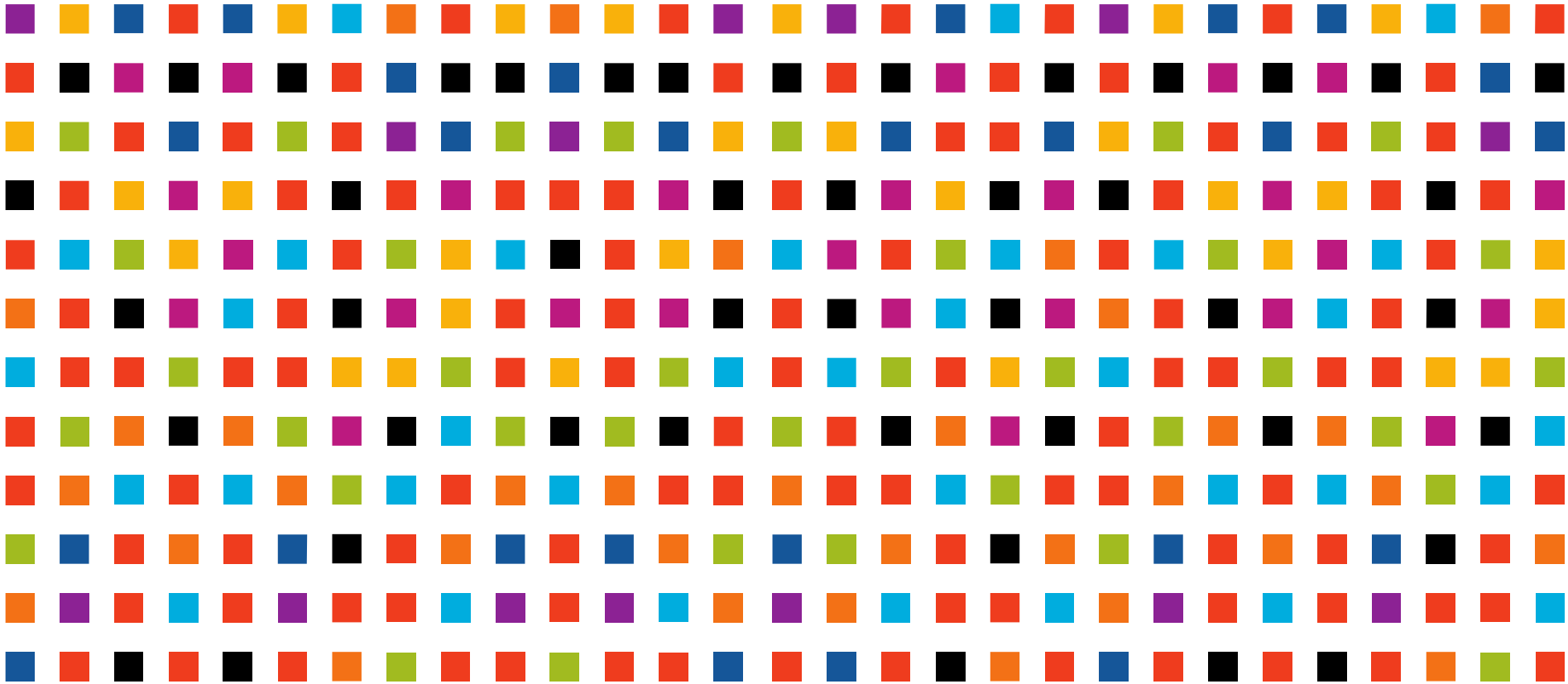

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