

***Pattern of striatal neurons pyroptosis in the  
R6/2 mouse model of Huntington's disease***

*55<sup>o</sup> Congresso Associazione Italiana Neuropatologia e Neurobiologia Clinica*

*45<sup>o</sup> Congresso Associazione Italiana Ricerca Invecchiamento Cerebrale*



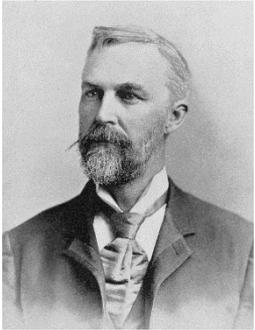
**23-25 Maggio 2019, Bologna**

**SANTA LUCIA**  
NEUROSCIENZE  
E RIABILITAZIONE

**Relatore**  
**EMANUELA PALDINO**

23 Maggio 2019

# Huntington's disease



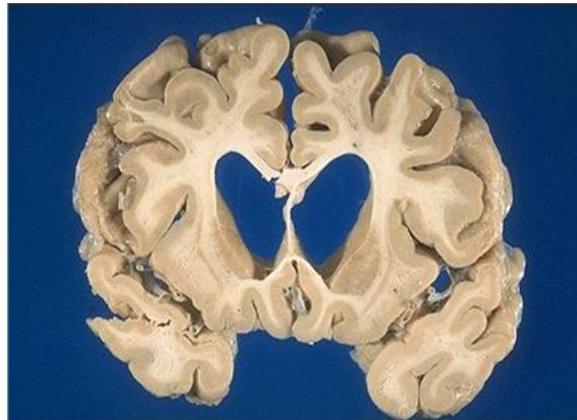
" When either or both of the parents have shown manifestations of the disease . . . one or more of the offspring invariably suffer of the disease, if they live to adult life. But if by any chance these children go through life without it, the thread is broken and the grandchildren and great-grandchildren of the original shakers may rest assured that they are free from disease."  
(Huntington, 1872)

*Huntington's disease is an autosomal dominant neurodegenerative disorder due to an expansion of a trinucleotide repeat in IT15 gene encoding for the protein huntingtin (Albin & Tagle,1995).*

*The neurodegenerative disease is characterized by motor dysfunction, cognitive decline and psychiatric disorders.*



WT



HD

## *Striatal Interneurons*

**Cholinergic**

**Somatostatin-NPY-NOS containing**

**Parvalbuminergic**

**Calretininergic**

## *Striatal Projection Neurons*

**Calbindinergic**



# *HD pathology is characterized by the formation of intranuclear inclusions of mutated huntingtin, NIs (Di Figlia et al.,1997)*

## *Pathophysiology of HD*

### **GAIN OF FUNCTION**

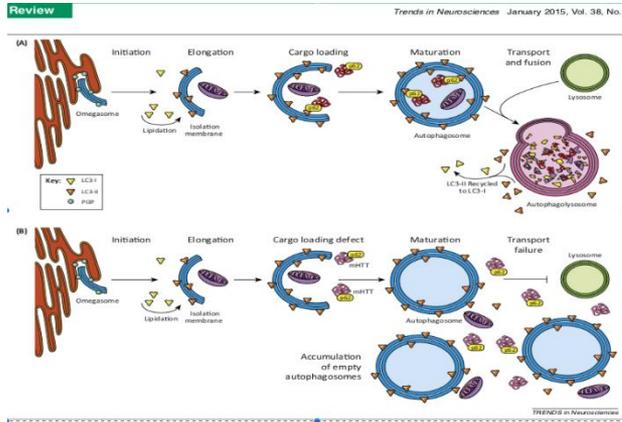
- ◆ Formation of intranuclear inclusions of mutated huntingtin (DiFiglia et al., 1997)
- ◆ Mitochondrial damage/ oxidative stress/Excitotoxicity

### **LOSS OF FUNCTION**

- ◆ Deprivation of neurotrophic factors (BDNF)
- ◆ Decreased anti-apoptotic factors



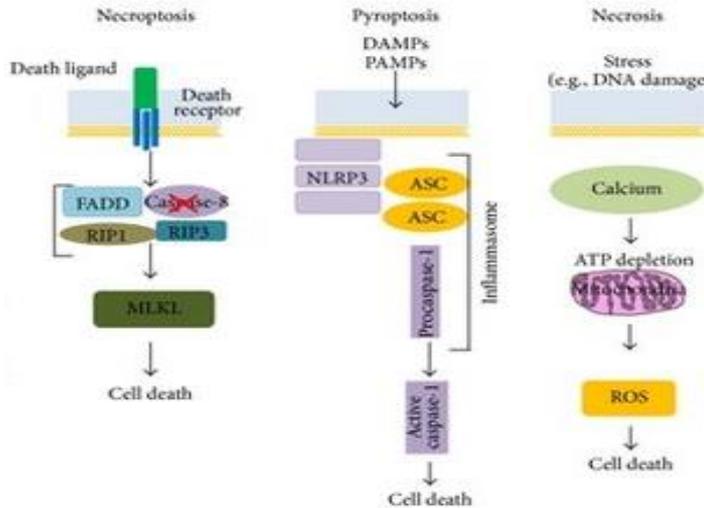
# Huntington's disease



Autophagy is altered in Huntington's disease

Autophagy involves the formation of double-membraned vesicles that incorporate damaged organelles, toxic or aggregated proteins and fuse with lysosome for degradation.

In HD autophagy is affected at several steps including a defect in cargo loading, trafficking of autophagosomes and decreased fusion between autophagosomes and lysosomes leading to a build-up of toxic materials in the cytoplasm and empty autophagosomes.



## Study's aim

- *Neuroinflammation has been shown as an essential factor in the pathogenesis of neurodegenerative diseases, such as Huntington's disease. Furthermore, activated microglia and increased pro-inflammatory cytokines are the major hallmarks in neurodegenerative diseases.*
- *In this study, we aimed at describing the involvement of pyroptosis and its distribution in the R6/2 mouse model of HD.*



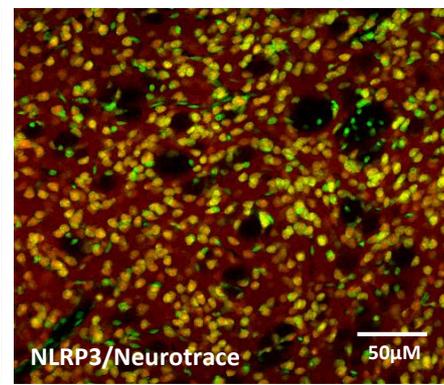
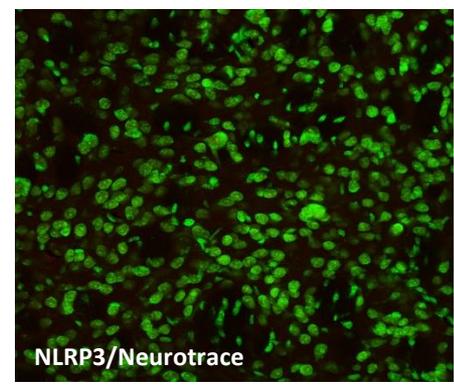
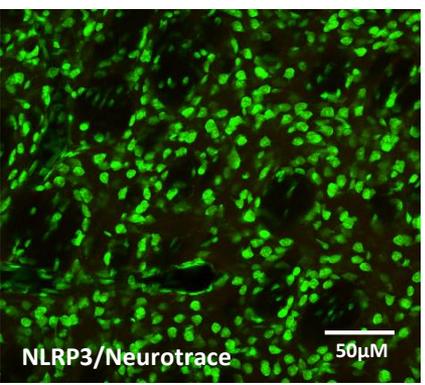
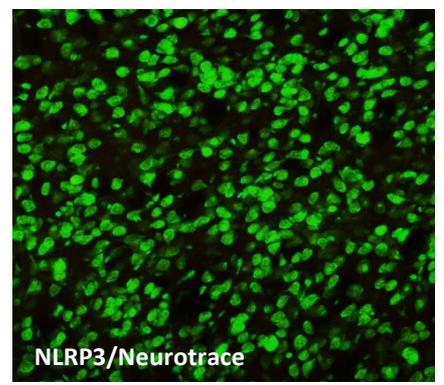
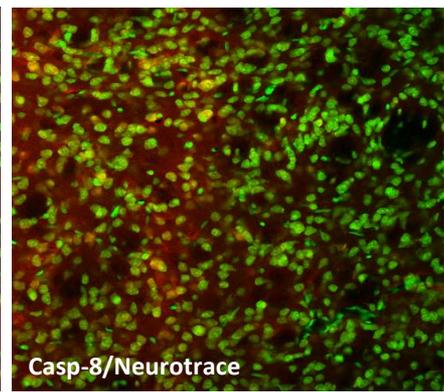
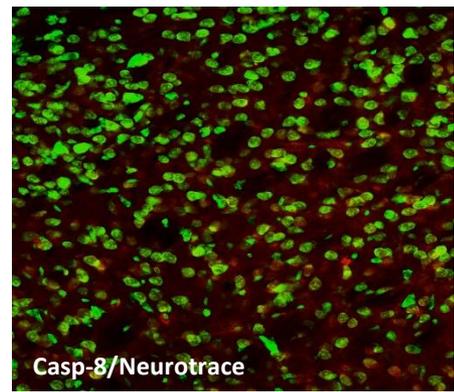
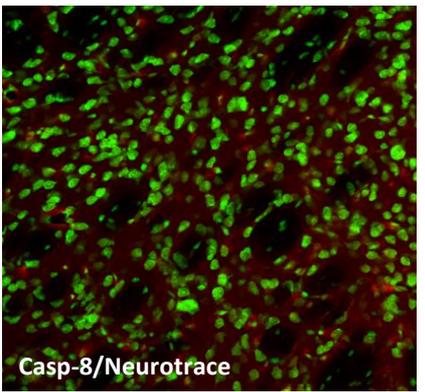
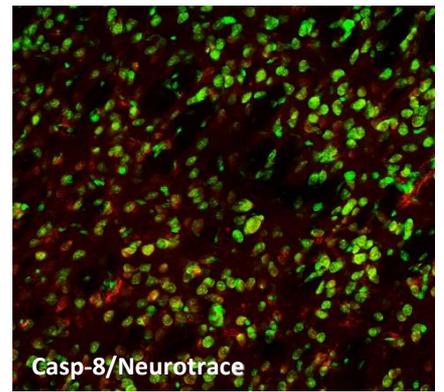
# Results

Wt 5weeks

Wt 13weeks

R6/2 5weeks

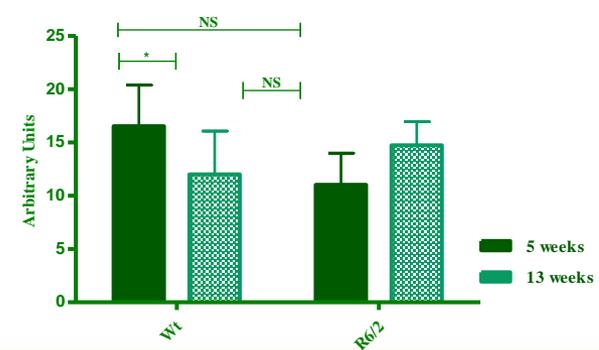
R6/2 13weeks



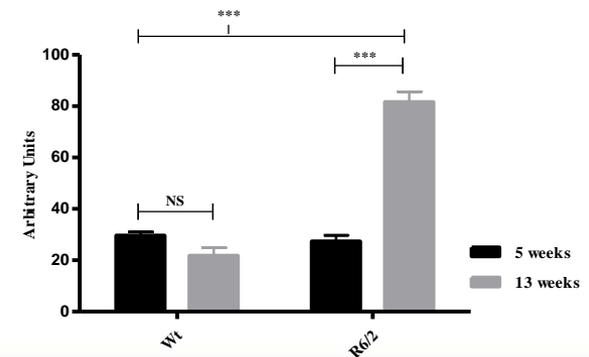
Casp-8/Neurotrace

NLRP3/Neurotrace

CASP8 immunoreaction intensity

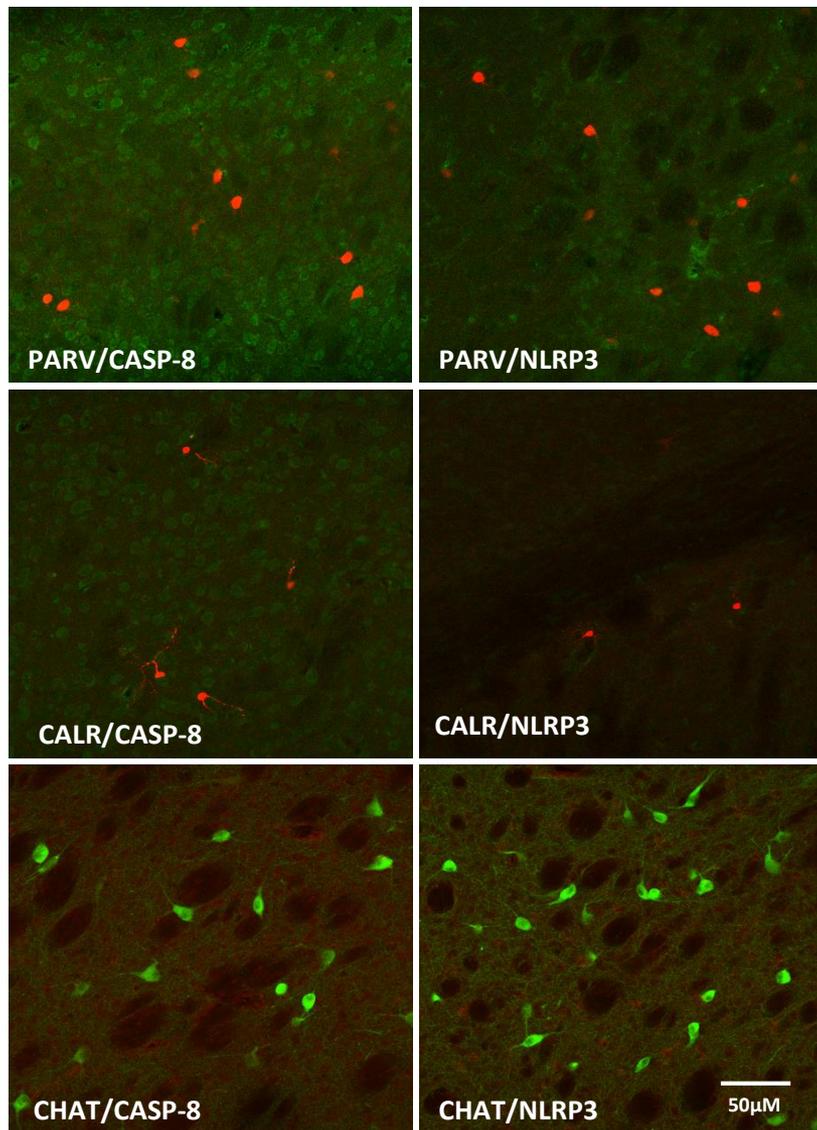


NLRP3 immunoreaction intensity

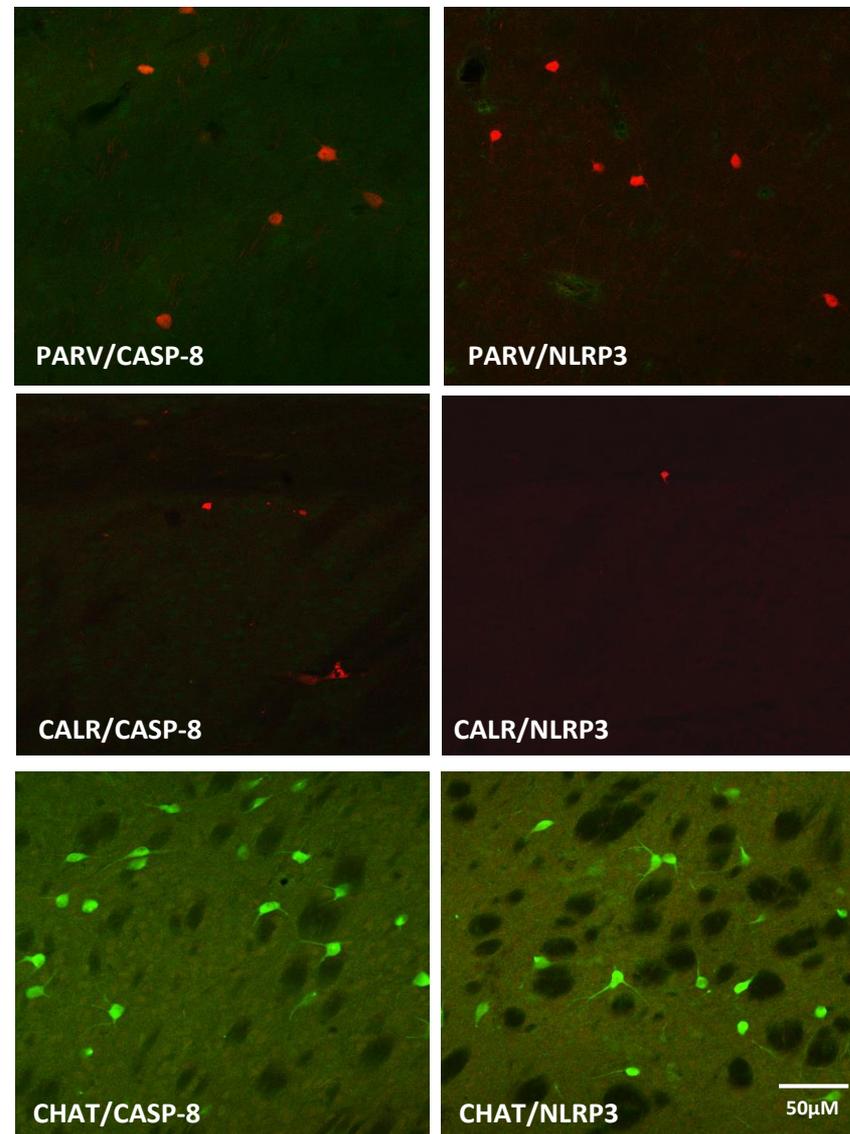


# Results

Wt 5weeks



Wt 13weeks

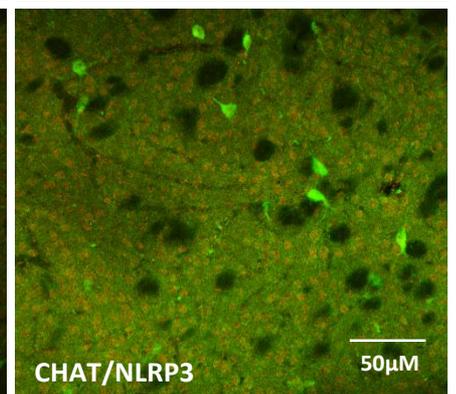
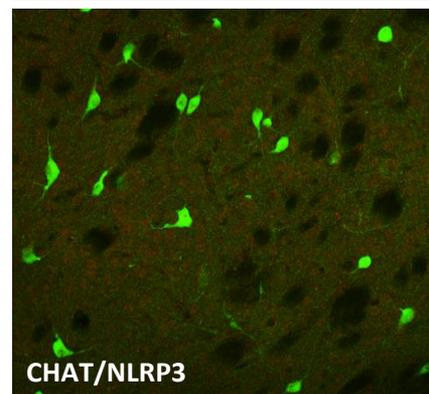
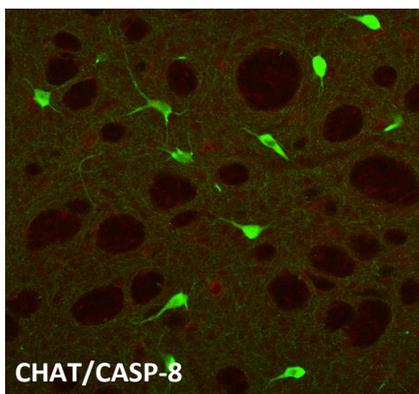
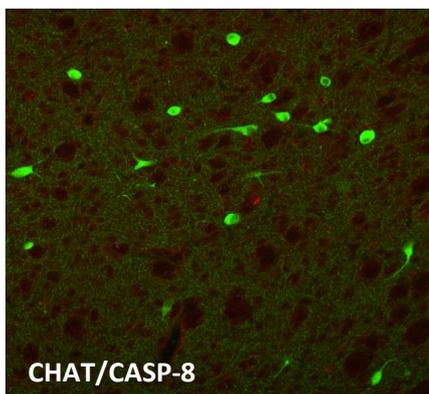
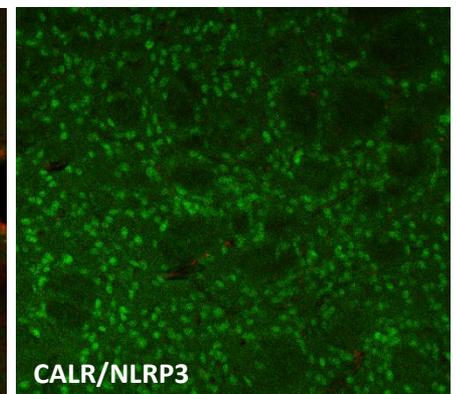
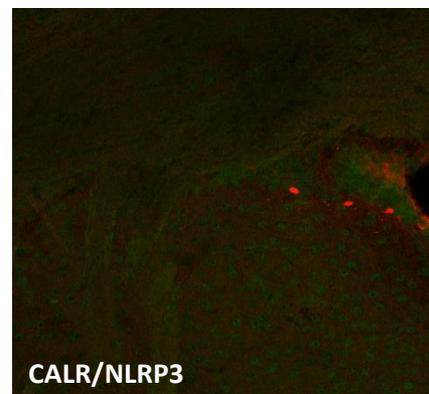
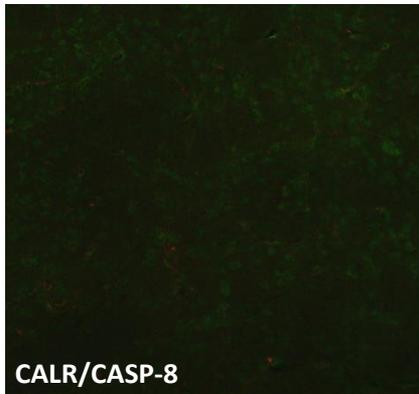
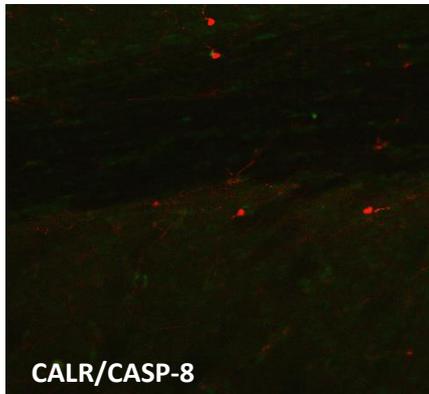
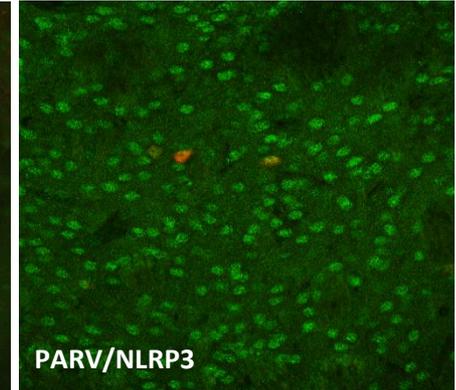
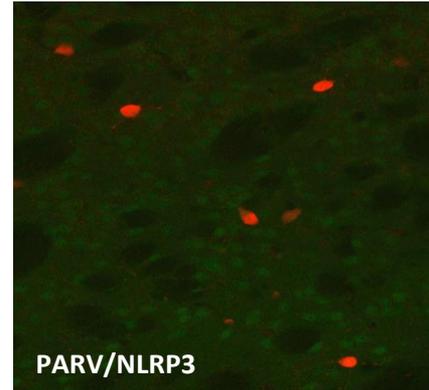
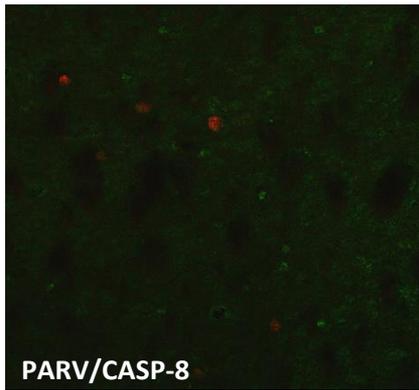
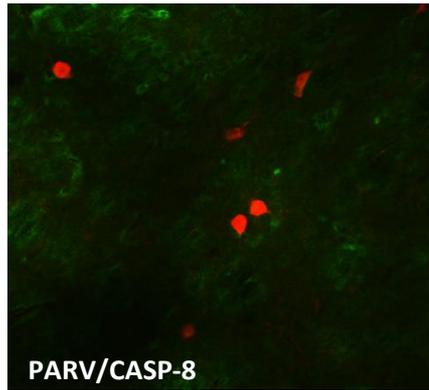


R6/2 5weeks

R6/2 13weeks

R6/2 5weeks

R6/2 13weeks



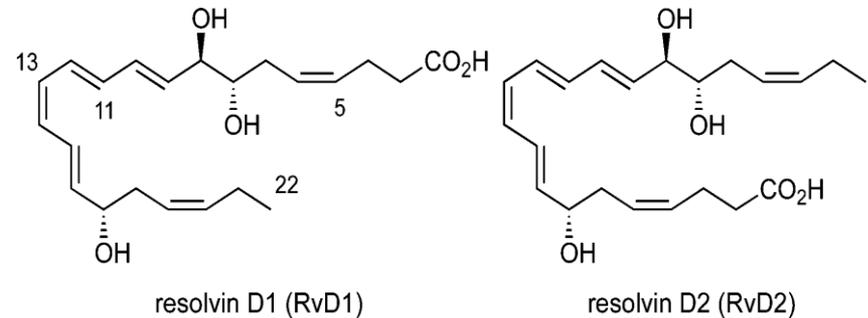
*R6/2 show an increase of NLRP3 content that colocalizes in PV-positive interneurons*

*NLRP3 expression doesn't affect CHAT positive interneurons*

# Conclusions

- *Previous data reveal that most R6/2 striatal cells displayed NLRP3 particularly in the later stages of the disease, where pyroptosis prevailed over apoptosis.*
- *Colocalization of NLRP3 and Parvalbumin containing neurons was observed in R6/2 at 13 weeks of age.*
- *Further studies are necessary to elucidate the impact of pyroptosis in HD, in order to develop more sophisticated strategies aimed at fighting neurodegeneration.*

**PYROPTOSIS**





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