Immunoproteasome in neuroinflammation

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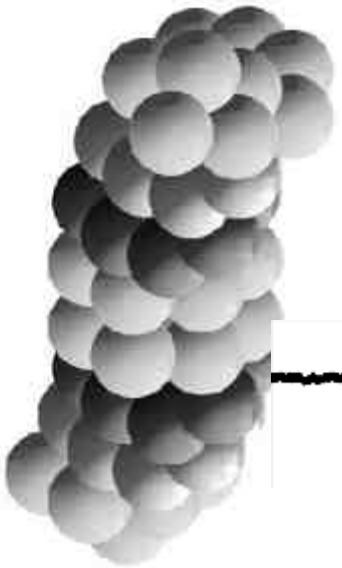
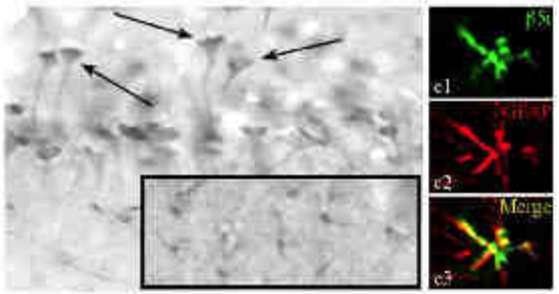
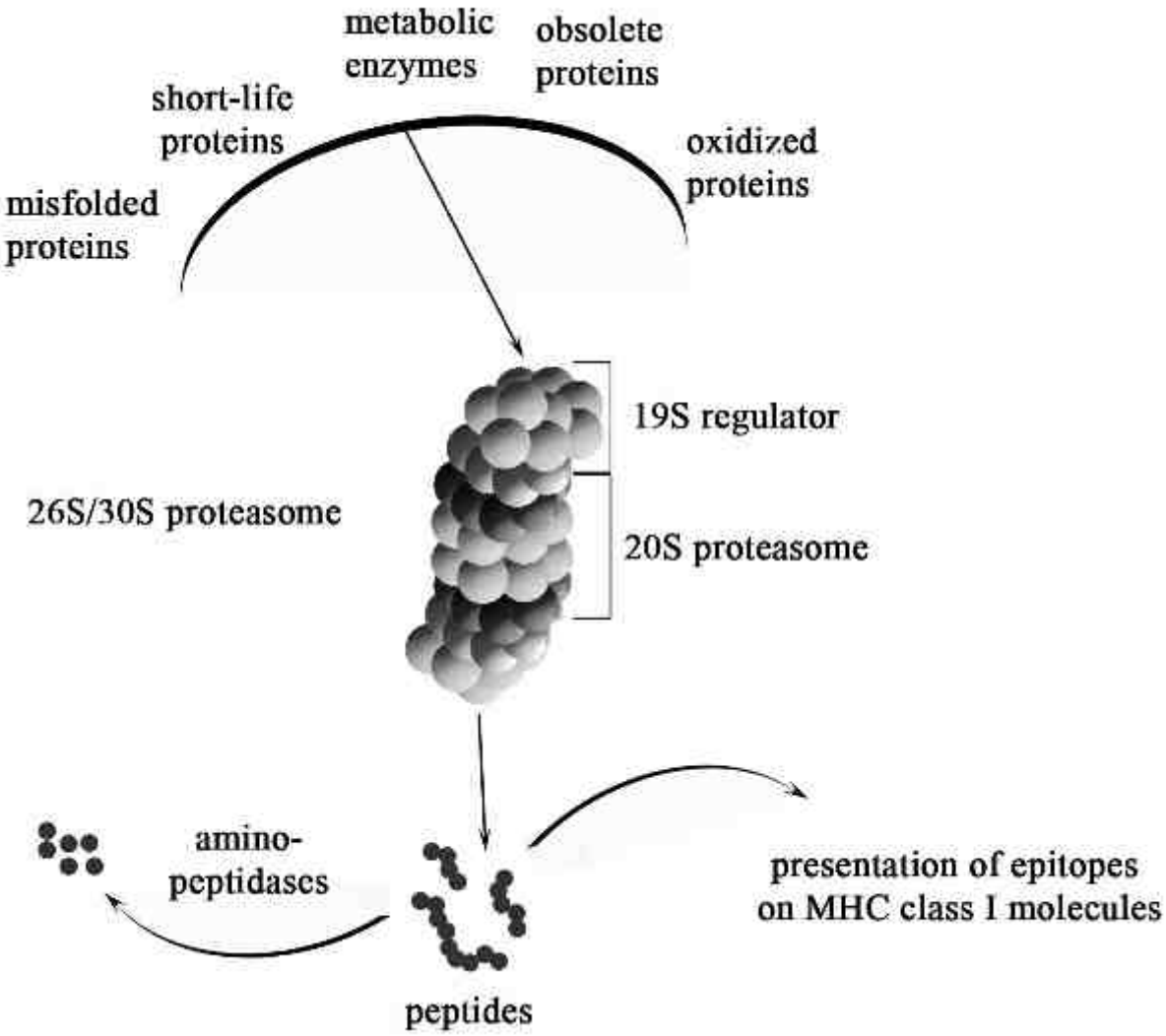


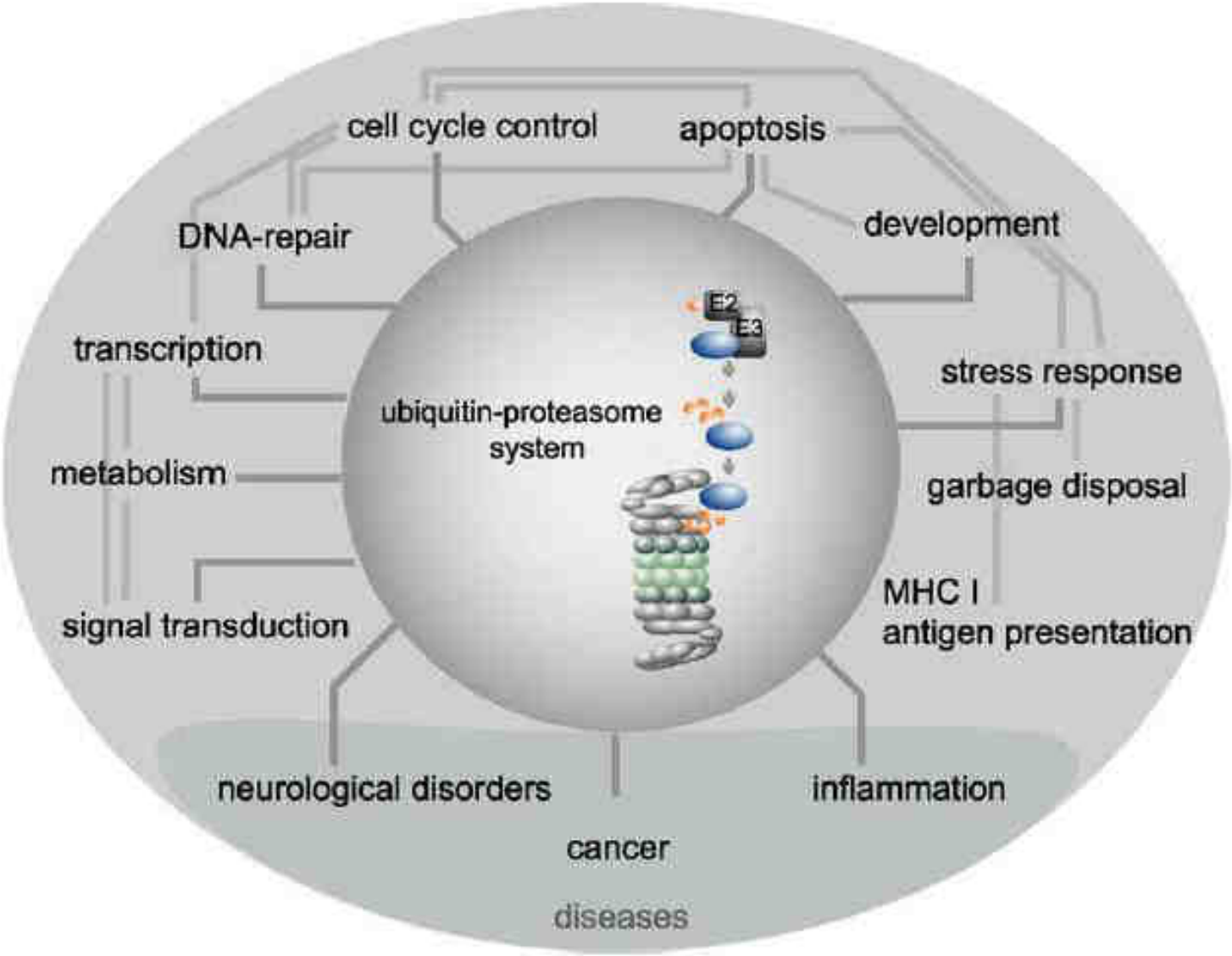


Protein targets of the Ubiquitin-proteasome system (UPS)



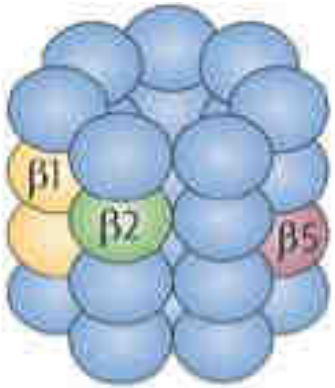
Bellavista et al, 2014

Functions of UPS



Wolf and Hilt, 2004

Proteasome isoforms

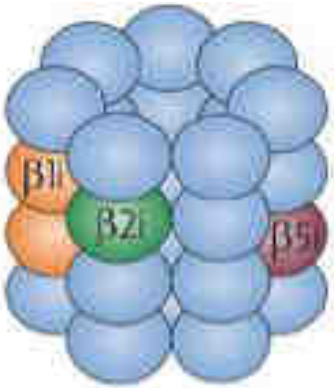


Constitutive proteasome

β1 (PSMB6, Y, δ)

β2 (PSMB7, Z, MC14)

β5 (PSMB5, X, MB1, ε)

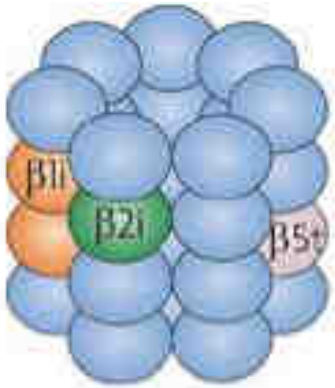


Immunoproteasome

β1i (PSMB9, LMP2)

β2i (PSMB10, LMP10, MECL1)

β5i (PSMB8, LMP7)



Thymoproteasome

β1i (PSMB9, LMP2)

β2i (PSMB10, LMP10, MECL1)

β5t (PSMB11)

Catalytic subunits

Quantitatively different cleavage specificity makes immunoproteasome specifically involved in:

Cytokine-mediated inflammation

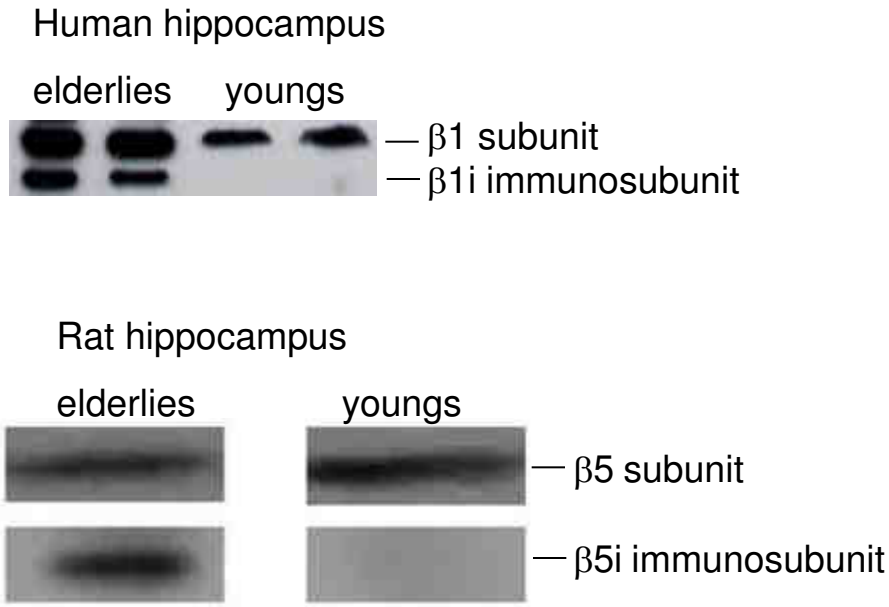
Cell-mediated immune response and lymphoid cell repertoire

Antigen presentation

Groettrup et al., 2010; Mishto et al., 2014

Immunoproteasome in CNS upon ageing

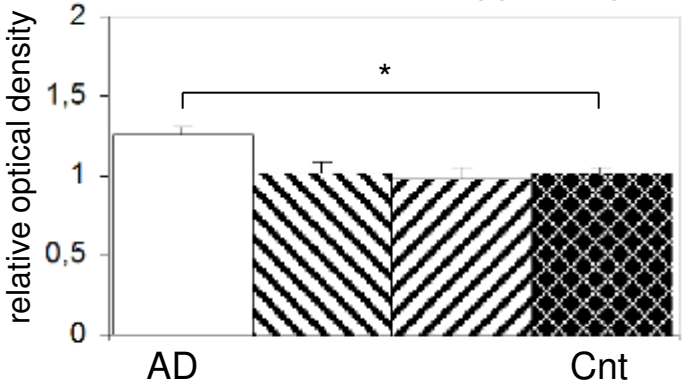
Immunoproteasome is almost absent in healthy young CNS but it is expressed in CNS upon ageing



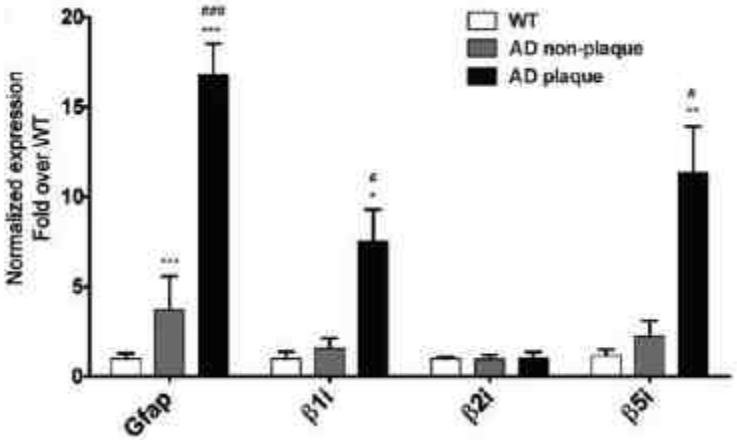
Mishto et al., 2006; Giannini et al., 2013

Immunoproteasome in Alzheimer disease

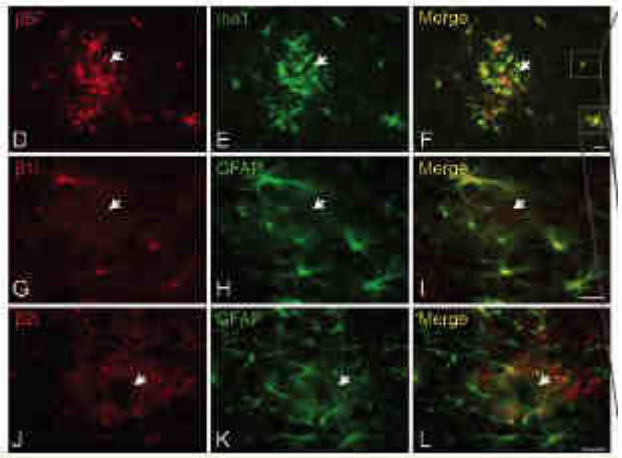
β1i immunosubunit - Human hippocampus



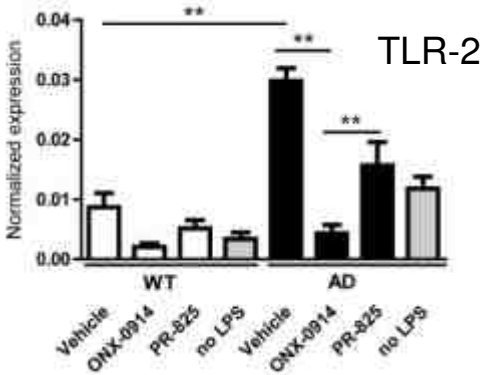
wt *vs* APPswePS1dE9 mouse hippocampus

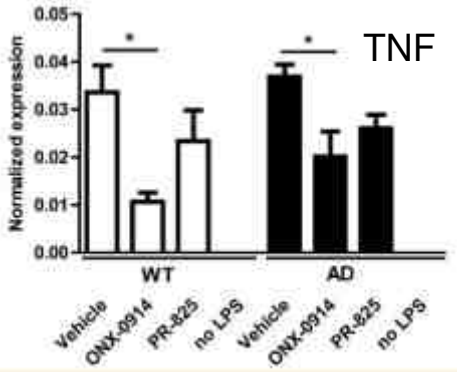


Immunoproteasome expression in microglia and astrocytes



Immunoproteasome β5i inhibition reduces pro-inflammatory signalling in AD microglia



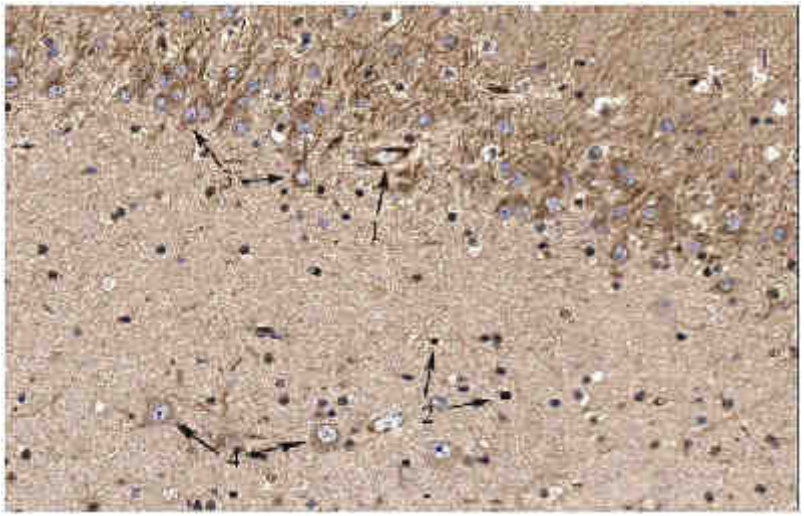


Mishto et al., 2006; Orre et al., 2013

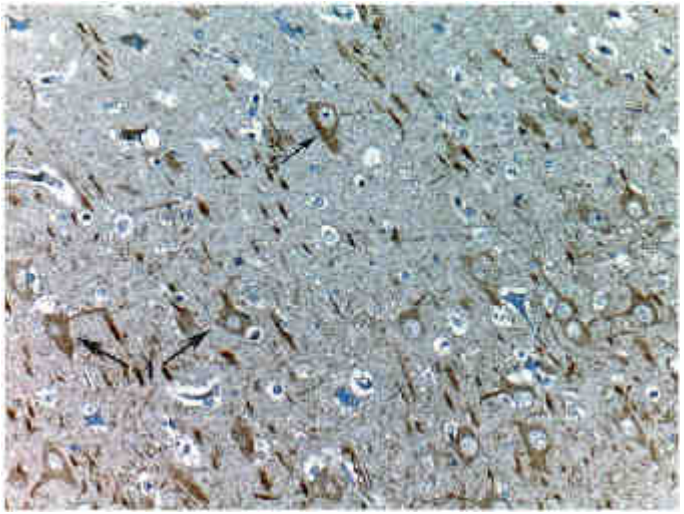
Immunoproteasome in pharmacoresistant epilepsies

Human FCD / TLE hippocampus

Focal cortex dysplasia - β1i immunosubunit



Mesial temporal lobe epilepsy - β5i immunosubunit

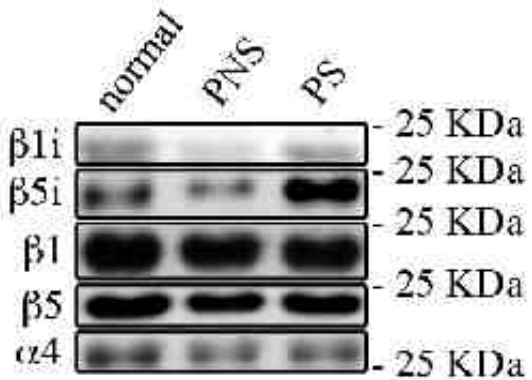


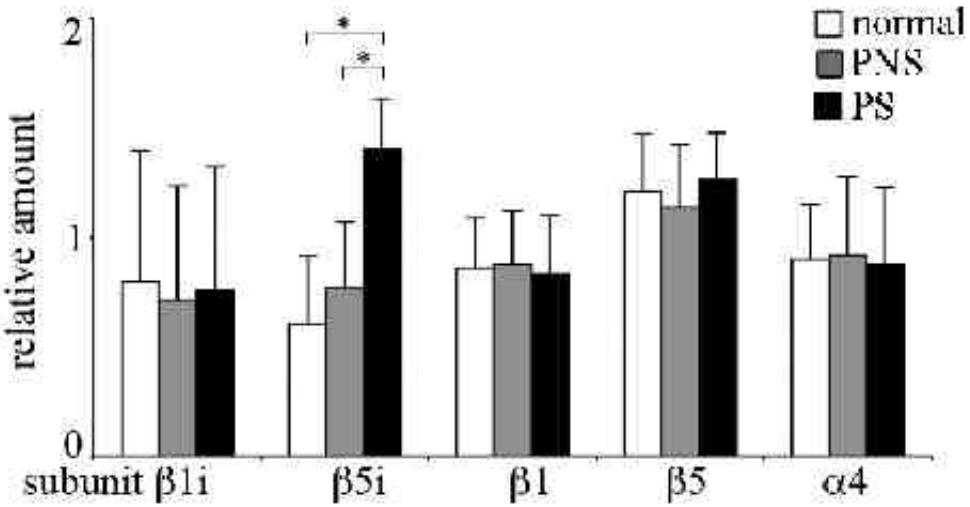
1. Endotelial cells
2. Glia
3. Granular neurons
4. Pyramidal neurons

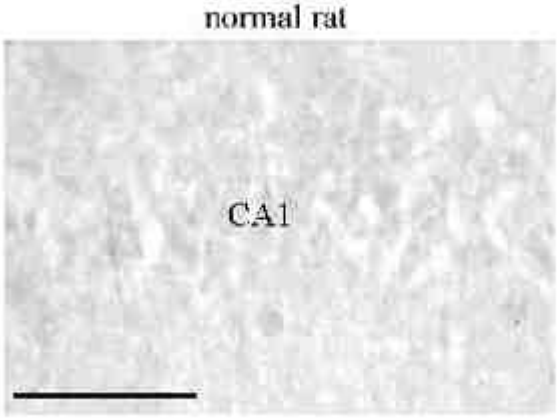
Mishto et al., 2010

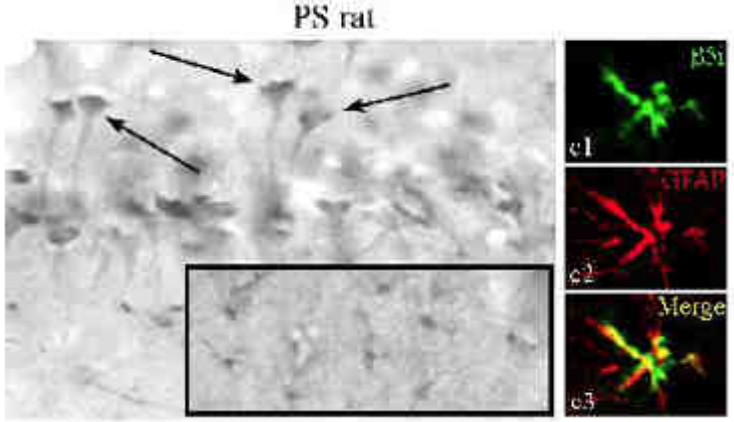
Immunoproteasome in pharmacoresistant epilepsies

Pilocarpine-induced epileptic rat hippocampus









Neurons
Astrocytes

Mishto et al., 2015

Immunoproteasome in pharmacoresistant epilepsies

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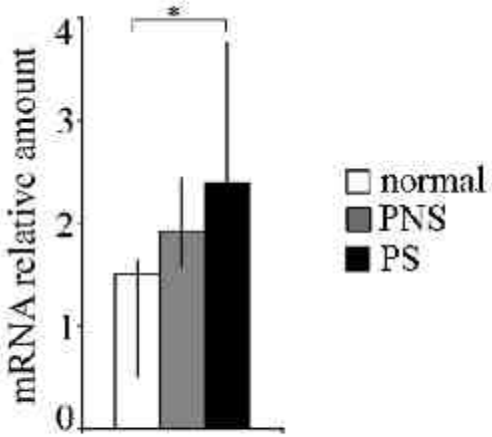
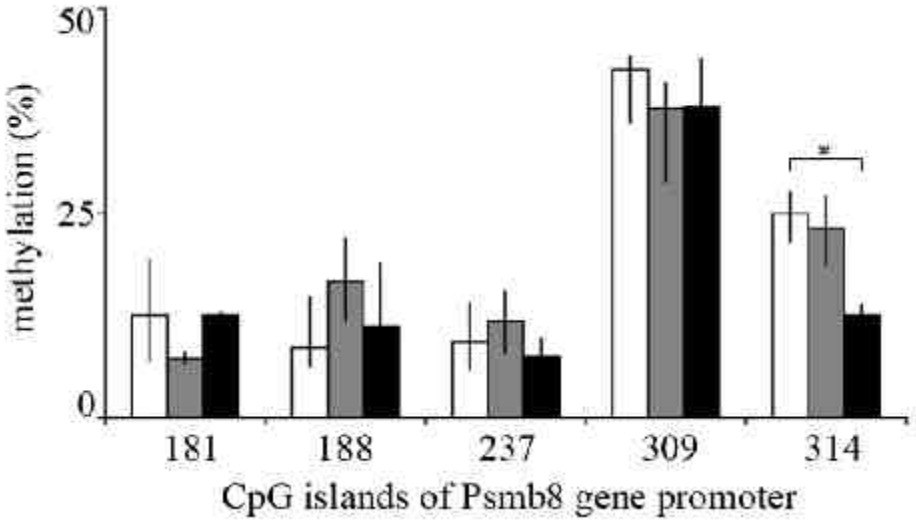
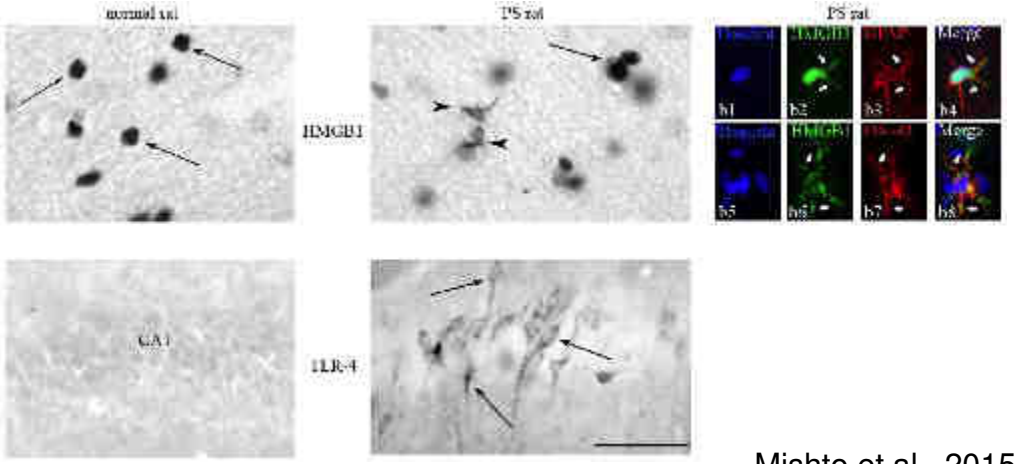




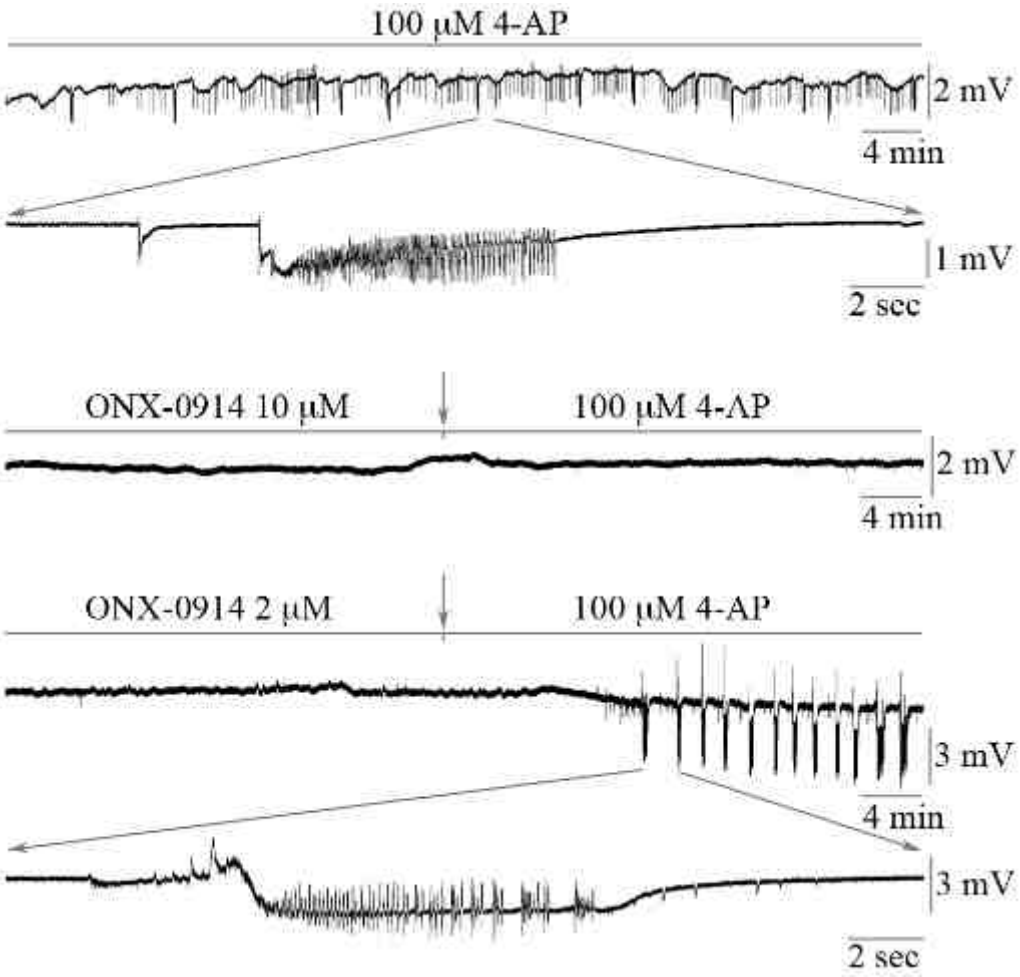
HMGB1-mediated activation of TLR-4 leads to immunoproteasome expression



Mishto et al., 2015

Immunoproteasome in pharmacoresistant epilepsies

Pilocarpine-induced epileptic rat hippocampus



Mishto et al., 2015

Immunoproteasome in pharmacoresistant epilepsies

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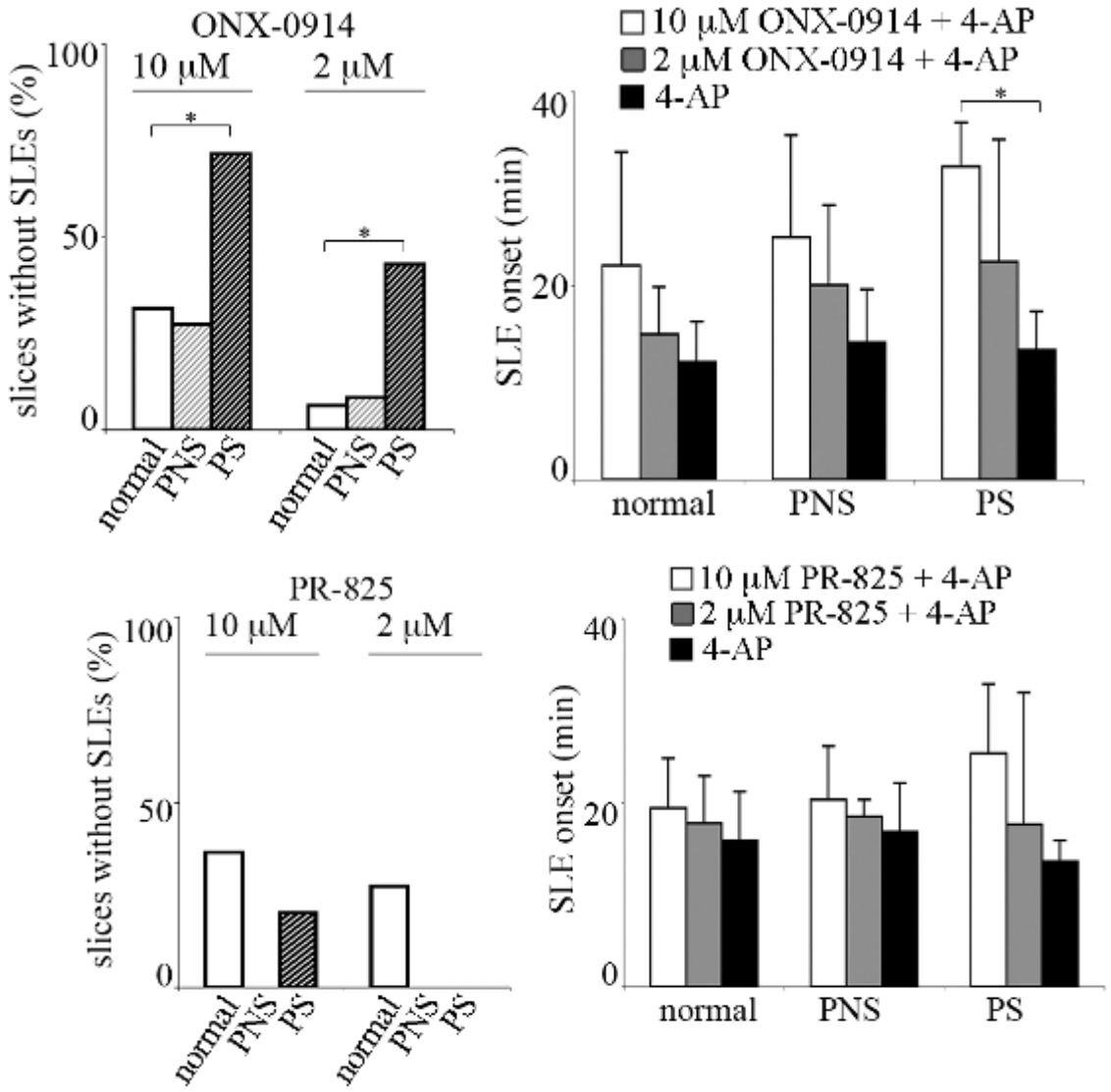


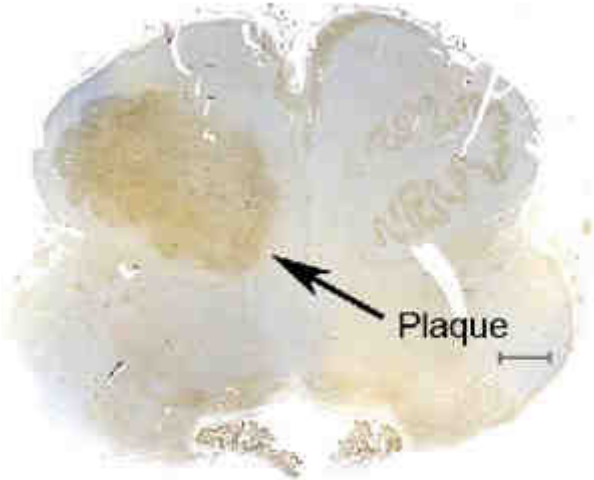
β5i immunosubunit inhibition suppresses or delayes SLEs in epileptic rats

β5 subunit inhibition has no or mild effects on SLEs in epileptic rats

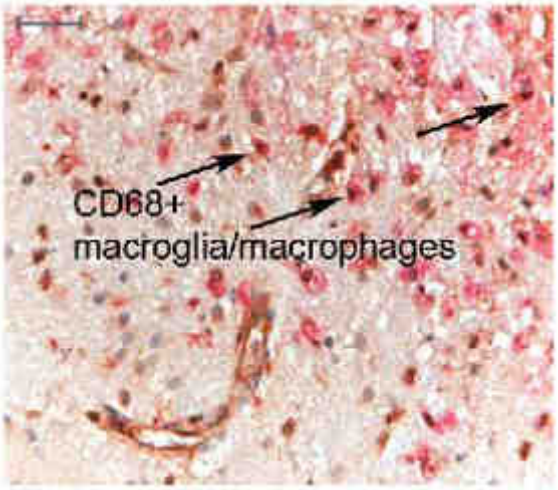
Mishto et al., 2015

Immunoproteasome in multiple sclerosis

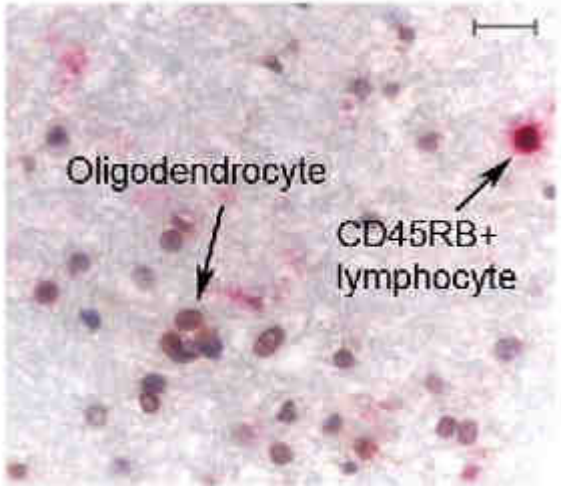
Staining of β1i immunosubunit



Rostral medulla with MS palques



Parietal lobe of MS patient

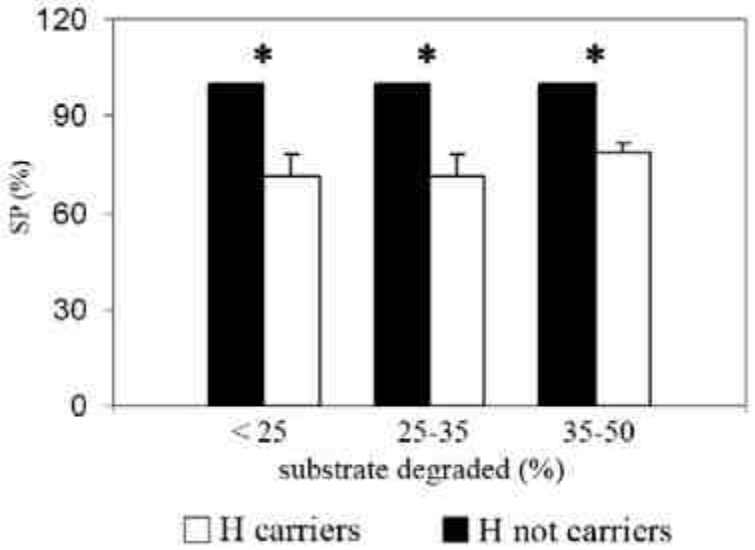


Mishto et al., 2010

Effect by acting on myelin antigen presentation?

Genotype	MS (n = 337)	control (n = 202)	p	OR (95% CI)
HH	26 (7.7)	32 (15.8)		
RH	146 (43.3)	80 (39.6)	0.013	
RR	165 (49.0)	90 (44.6)		
HH vs RR			0.005	0.443 (0.249–0.790)
HH vs RH			0.006	0.445 (0.248–0.799)

HLA-A*0201+ subjects carrying the 60H polymorphism in β1i immunosubunit are less prone to develop MS

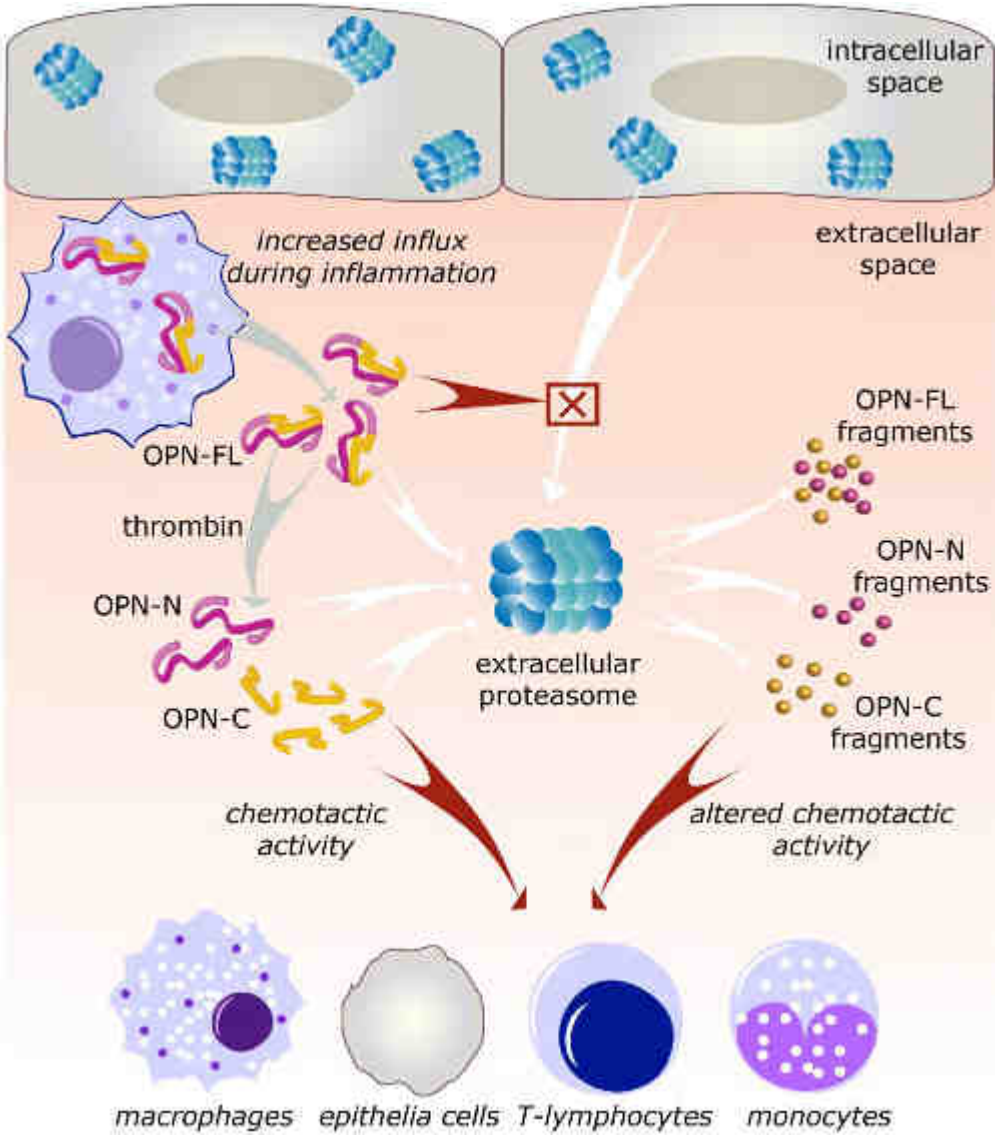


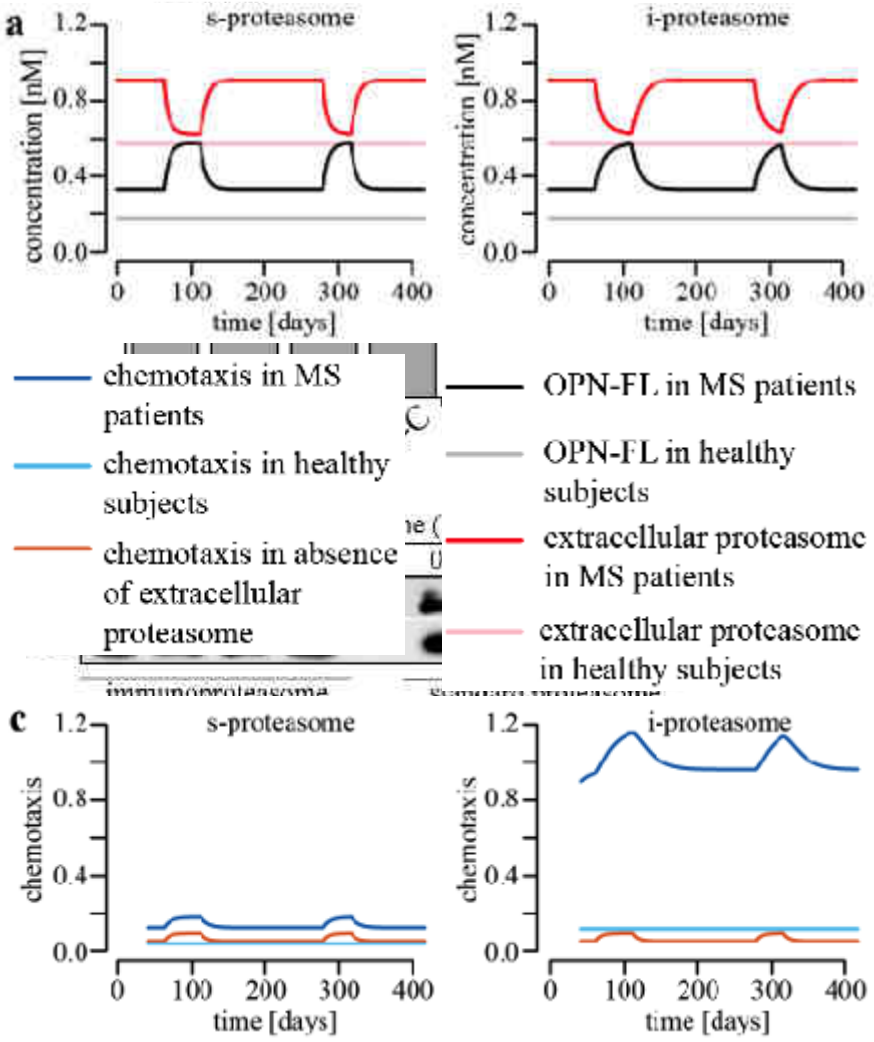
In vitro production of HLA-A*0201-restricted **$MBP_{111-119}$ epitope** by $60H^+$ or $60H^-$ β1i immunosubunit

Mishto et al., 2010

Immunoproteasome in multiple sclerosis

Effect by acting on cytokine circuits?





Bellavista et al., under review

Summary

Immunoproteasome expression is induced in different CNS cell types:

- during ageing
- in AD patients
- in epileptic patients
- in Multiple Sclerosis patients

Immunoproteasome expression is involved in neuropathologies in:

- cytokine-mediated inflammation
- pathology-associated antigen presentation
- neuronal activity

The pathology-specific expression of immunoproteasome makes specific immunoproteasome inhibitors interesting for therapy.

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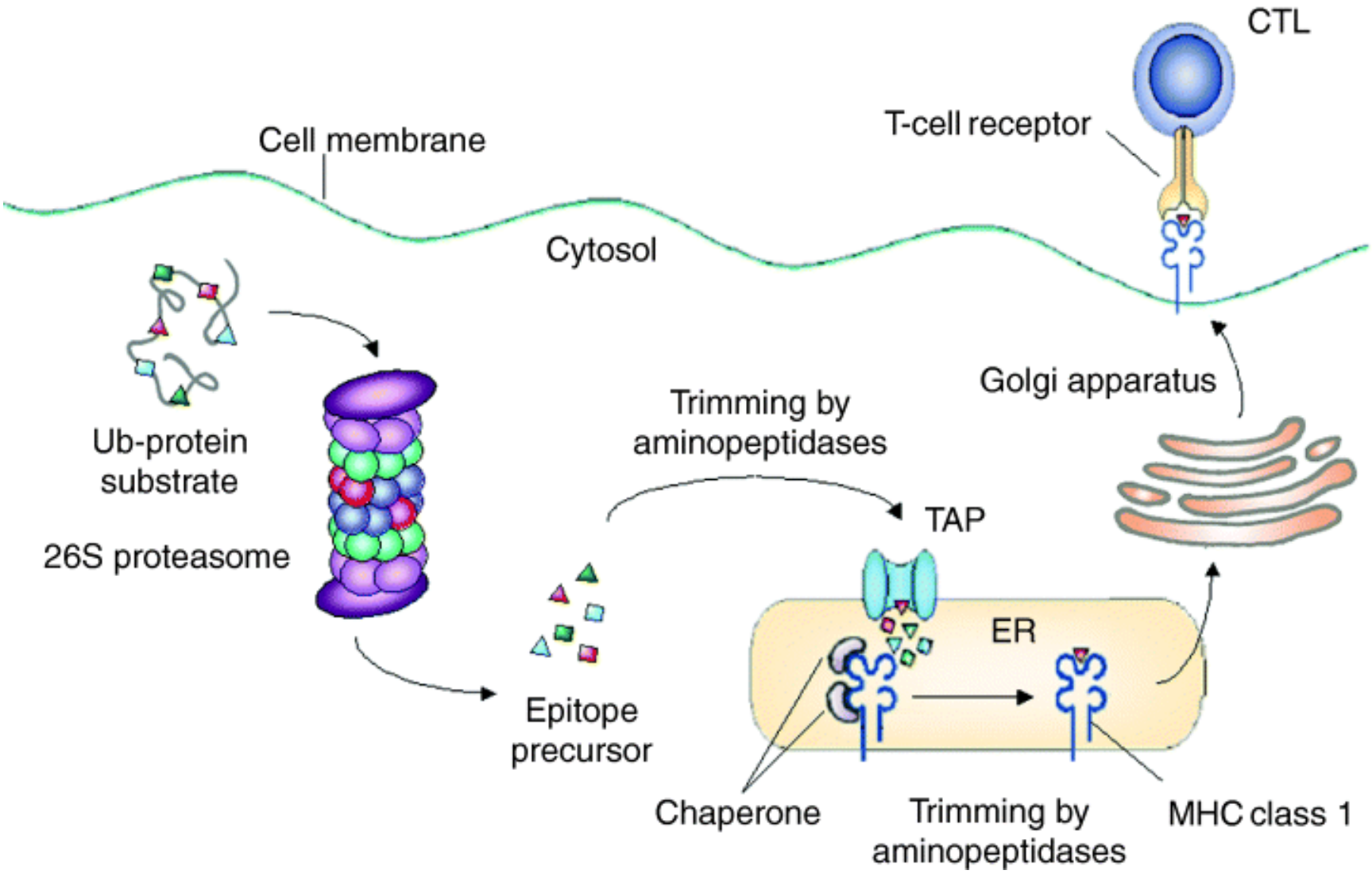
Proteasomes and antigens presentation



Strehl et al, 2005