



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

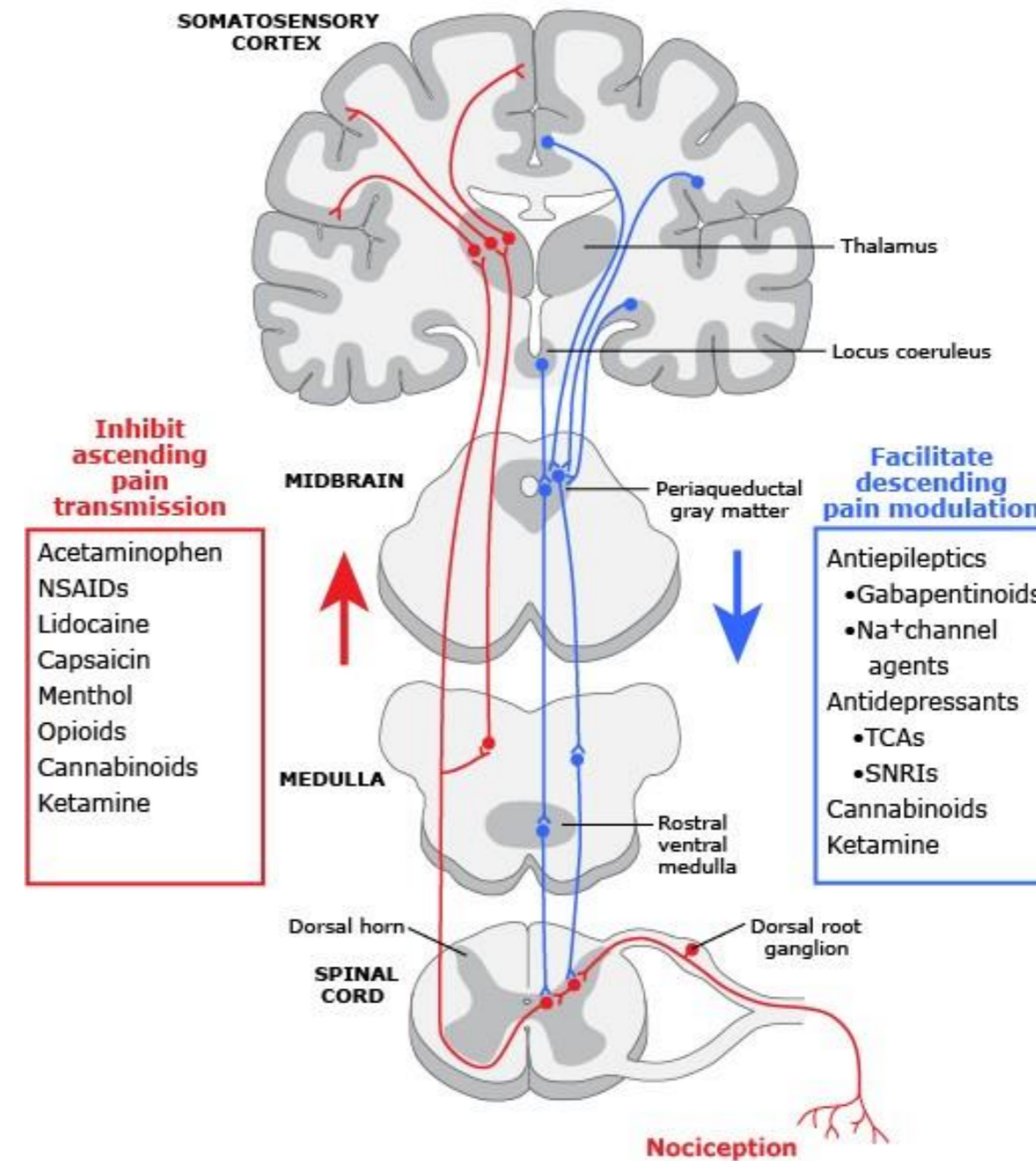
**Role of proKineticines in gene expression
alterations of KDMs and PPARs in a murine
model of bortezomib-induced peripheral
neuropathy**

Definizione secondo l'International Association for the Study of Pain (IASP):

“*un'esperienza sensoriale ed emozionale spiacevole associata a, o simile a quella associata, danno tissutale, in atto o potenziale*”

Allodinia Iperalgesia

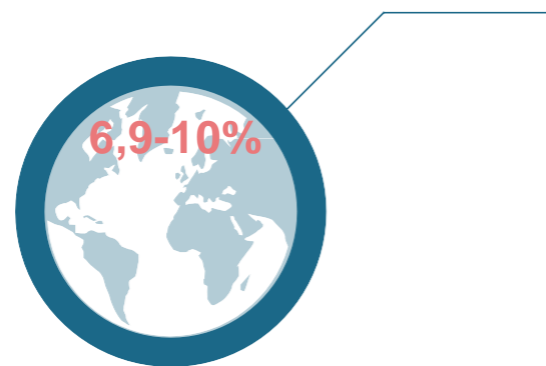
Il dolore origina in periferia a partire dai nocicettori attivati in seguito a diversi tipi di stimoli.



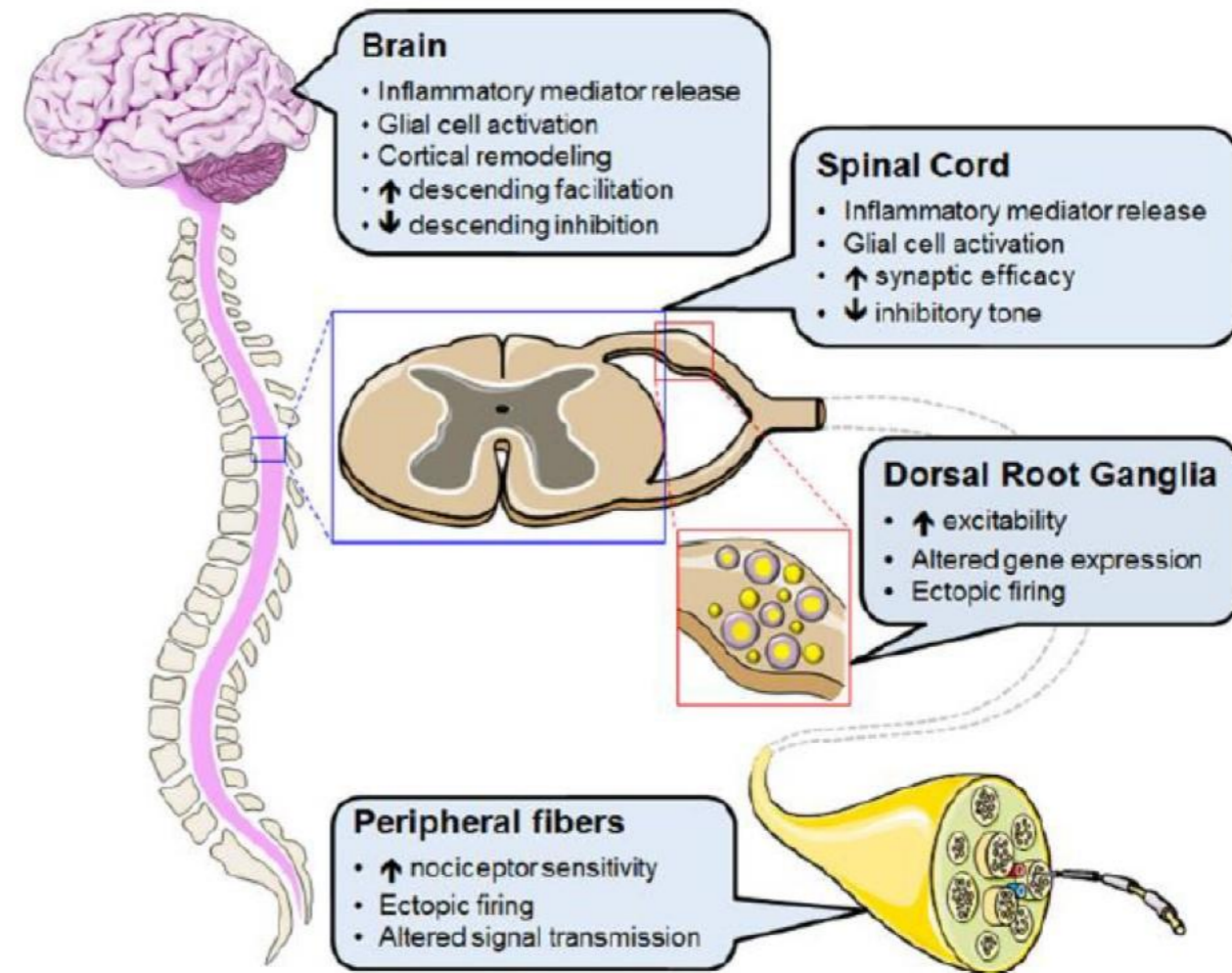
Si tratta di :

“ dolore causato da una lesione o da una patologia del sistema nervoso somatosensoriale. ”

(International Association for the Study of Pain)



Central sensitization



Peripheral sensitization

Neuropatia periferica indotta da chemioterapici (CIPN)

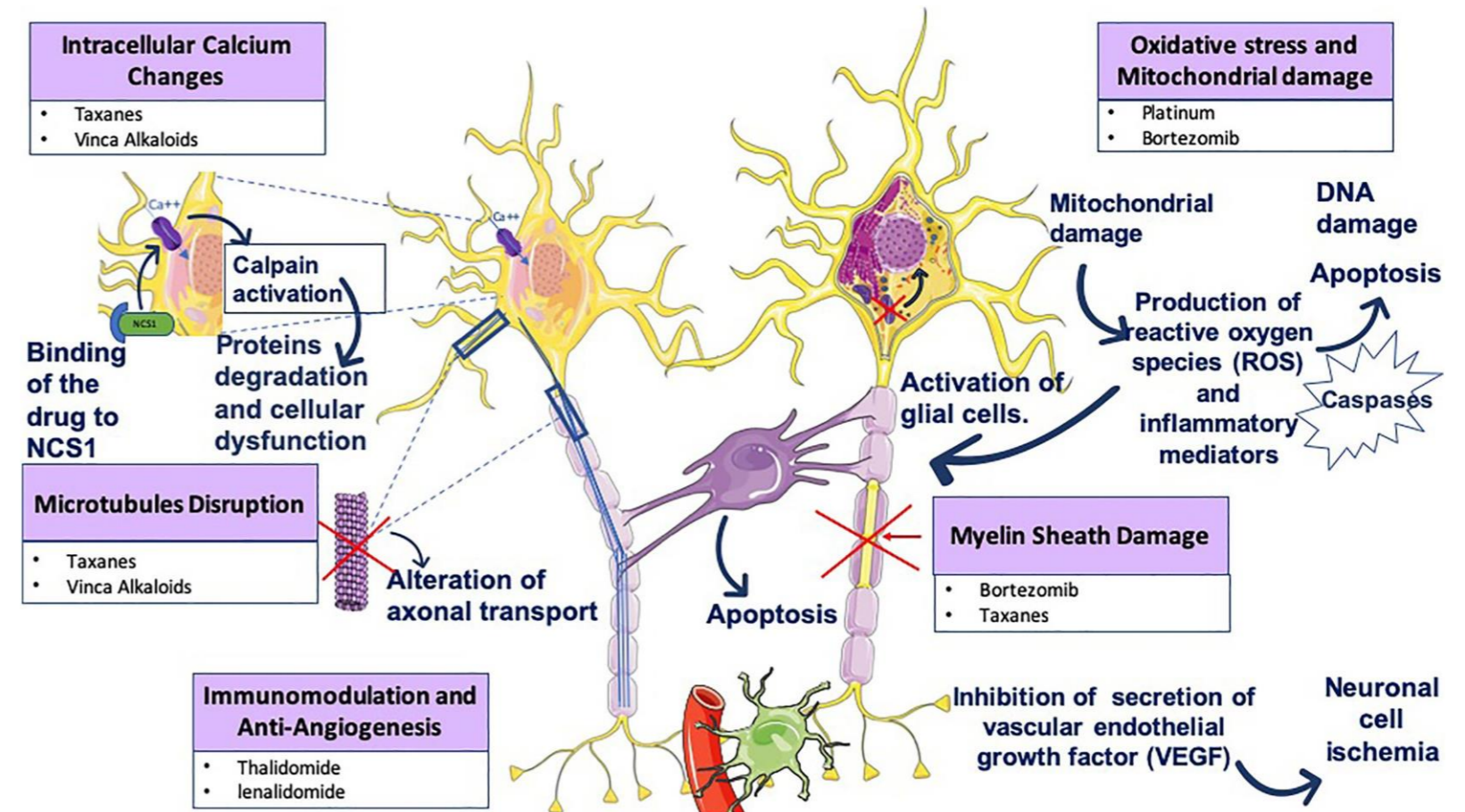
{/che-mio-te-rà-pi-ci/}

Alcaloidi della vinca : vincristina

Derivati del platino : oxaliplatino

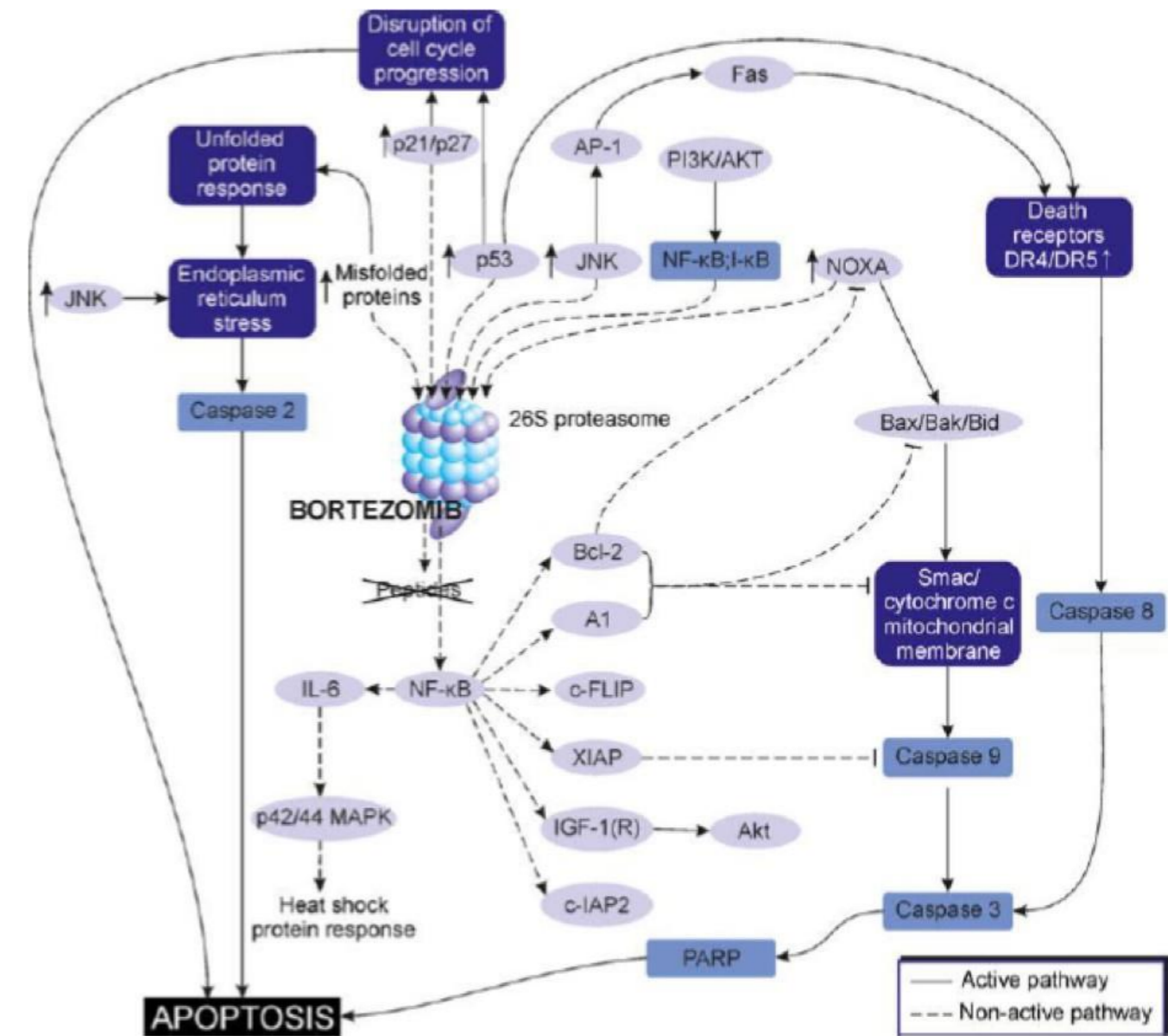
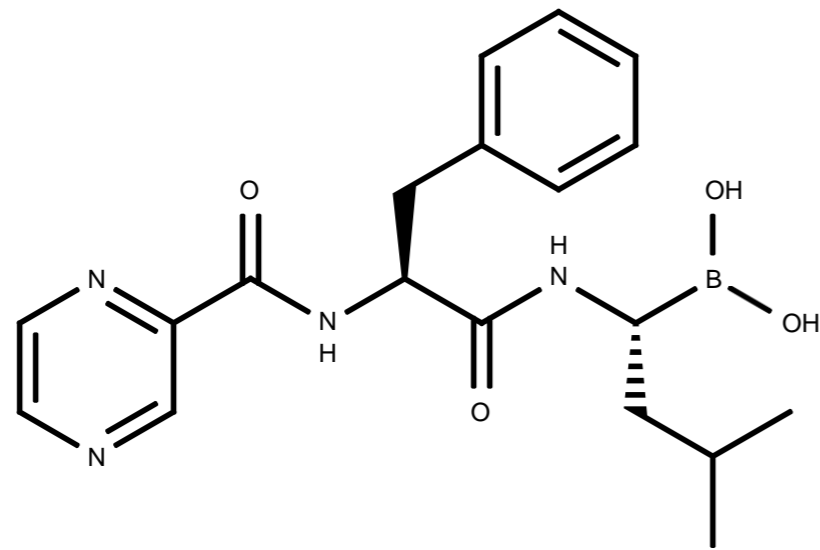
Tassani : paclitaxel

Inibitori del proteasoma : bortezomib



Bortezomib

Il bortezomib è stato approvato nel 2003, nel 2005 e nel 2008 dalla U.S. *Food and Drug Administration* per il trattamento del mieloma multiplo progressivo (MM) recidivo/refrattario, recidivo e di nuova diagnosi, rispettivamente.

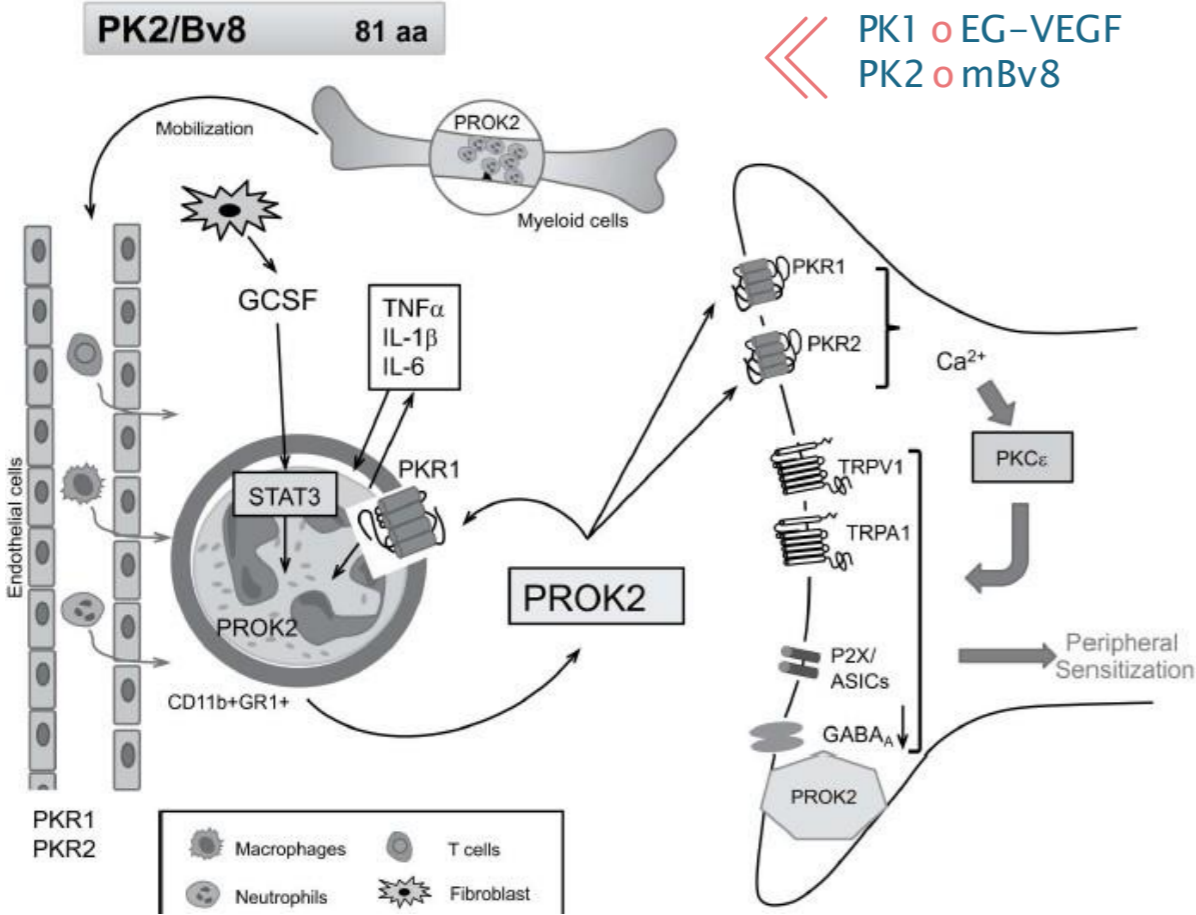


Meccanismo d'azione → Inibizione del proteasoma

Ruolo delle prochinetine nel dolore

Nei mammiferi sono state identificate:

PK1 o EG-VEGF
PK2 o mBv8



A Prokineticin-Driven Epigenetic Switch Regulates Human Epicardial Cell Stemness and Fate

REHANA QURESHI¹, MICHEL KINDO², MOUNIA BOULBERDAA¹, JEAN-JACQUES VON HUNOLSTEIN², MARJA STEENMAN³, CANAN G. NEBIGIL^{1,4}

Prokineticin 2 Upregulation in the Peripheral Nervous System Has a Major Role in Triggering and Maintaining Neuropathic Pain in the Chronic Constriction Injury Model

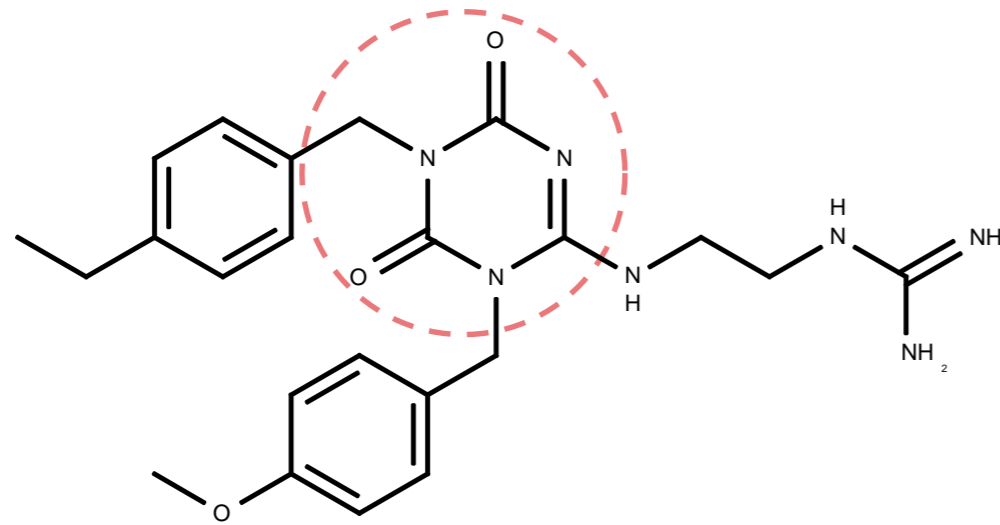
Roberta Lattanzi¹, Daniela Maftai¹, Veronica Marconi¹, Fulvio Florenzano², Silvia Franchi³, Elisa Borsani⁴, Luigi Fabrizio Rodella⁴, Gianfranco Balboni⁵, Severo Salvadori⁶, Paola Sacerdote³, and Lucia Negri¹

Targeting prokineticin system counteracts hypersensitivity, neuroinflammation, and tissue damage in a mouse model of bortezomib-induced peripheral neuropathy

Giorgia Moschetti¹, Giada Amodeo¹, Daniela Maftai², Roberta Lattanzi³, Patrizia Procacci⁴, Patrizia Sartori⁴, Gianfranco Balboni⁵, Valentina Onnis⁵, Vincenzo Conte⁴, Alberto Panerai¹, Paola Sacerdote¹ and Silvia Franchi^{1*}



PC1, antagonista del recettore per le prokineticine



Sequenza AVITGA N-terminale



porzione triazino-guadinica

Residuo di Trp in 24



porzione metossibenzilica

Prokineticin Receptor Inhibition With PC1 Protects Mouse Primary Sensory Neurons From Neurotoxic Effects of Chemotherapeutic Drugs *in vitro*

Giorgia Moschetti^{1*}, Theodora Kalpachidou², Giada Amodeo¹, Roberta Lattanzi³, Paola Sacerdote¹, Michaela Kress² and Silvia Franchi¹

PC1, a non-peptide PKR1-preferring antagonist, reduces pain behavior and spinal neuronal sensitization in neuropathic mice

F. Guida^{a,1}, R. Lattanzi^{b,1}, S. Boccella^a, D. Maftei^b, R. Romano^a, V. Marconi^b, G. Balboni^c, S. Salvadori^d, M.A. Scafuro^{a,e}, V. de Novellis^a, L. Negri^b, S. Maione^{a,**}, L. Luongo^{a,*}

Antagonism of the Prokineticin System Prevents and Reverses Allodynia and Inflammation in a Mouse Model of Diabetes

Mara Castelli¹, Giada Amodeo¹, Lucia Negri², Roberta Lattanzi², Daniela Maftei², Cecilia Gotti³, Francesco Pistillo³, Valentina Onnis⁴, Cenzo Congu⁴, Alberto E. Panerai¹, Paola Sacerdote^{1*}, Silvia Franchi¹

Recettori attivati dai proliferatori dei Perossisomi (PPARs) e dolore

Fattori di trascrizione ligando dipendenti appartenenti alla famiglia dei recettori nucleari.

Tre isoforme principali :

PPAR α
PPAR β/δ
PPAR γ

	Neuroanatomical locus	PPAR α	PPAR β/δ	PPAR γ
Peripheral	Dorsal root ganglion	✓ ^{b,c}	?	?
	C fibres	?	?	?
	A δ fibres	?	?	?
	A β fibres	?	?	?
Spinal	Spinal cord	✓ ^{a,d}	✓ ^d	✓ ^{a,d,g}
Supraspinal	Frontal cortex	✓ ^d	✓ ^d	✓ ^d
	Pre-frontal cortex (PFC)	✓ ^e	✓ ^e	✓ ^e
	Hippocampus	✓ ^d	✓ ^d	✓ ^d
	Thalamus	✓ ^d	✓ ^d	✓ ^d
	Hypothalamus	✗ ^d	✓ ^d	✓ ^d
	Basal ganglia	✓ ^{d,e}	✓ ^{d,e}	✓ ^{d,e}
	Amygdala	✓ ^e	✓ ^e	✓ ^e
	PAG	✓ ⁱ	?	✓ ⁱ
	Rostroventral medulla (RVM)	?	?	?
	Ventral tegmental area (VTA)	✓ ^e	✓ ^e	✓ ^e



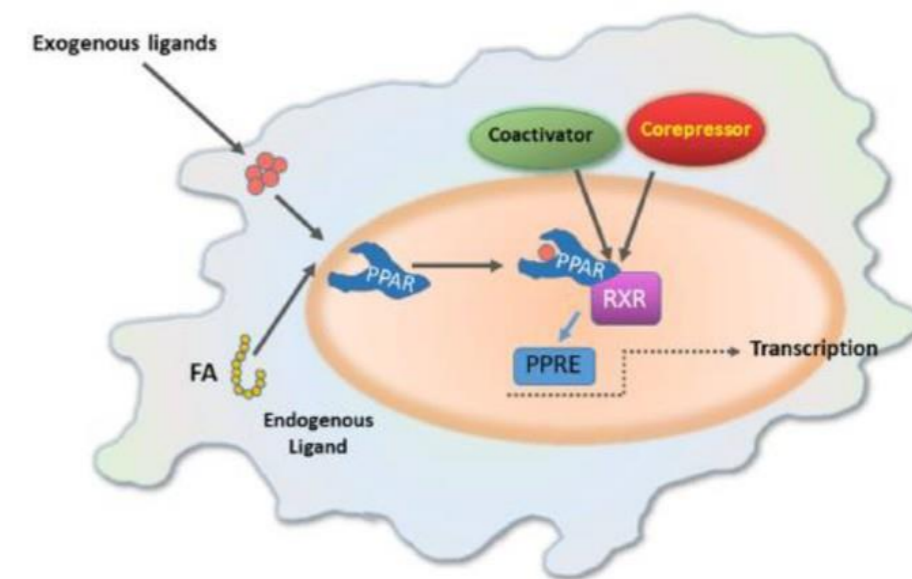
Central administration of palmitoylethanolamide reduces hyperalgesia in mice via inhibition of NF- κ B nuclear signalling in dorsal root ganglia

Giuseppe D'Agostino^a, Giovanna La Rana^a, Roberto Russo^a, Oscar Sasso^a, Anna Iacono^a, Emanuela Esposito^{a,d}, Giuseppina Mattace Raso^a, Salvatore Cuzzocrea^{c,d}, Jesse LoVerme^b, Daniele Piomelli^b, Rosaria Meli^a, Antonio Calignano^{a,*}



Intrathecal rosiglitazone acts at peroxisome proliferator-activated receptor γ to rapidly inhibit neuropathic pain in rats

Sajay B. Churi⁺, Omar S. Abdel-Aleem⁺, Kiranjeet K. Tumber, Heather Scuderi-Porter, and Bradley K. Taylor⁺



Ruolo dei meccanismi epigenetici nel dolore

Histone demethylase UTX/KDM6A enhances tumor immune cell recruitment, promotes differentiation and suppresses medulloblastoma

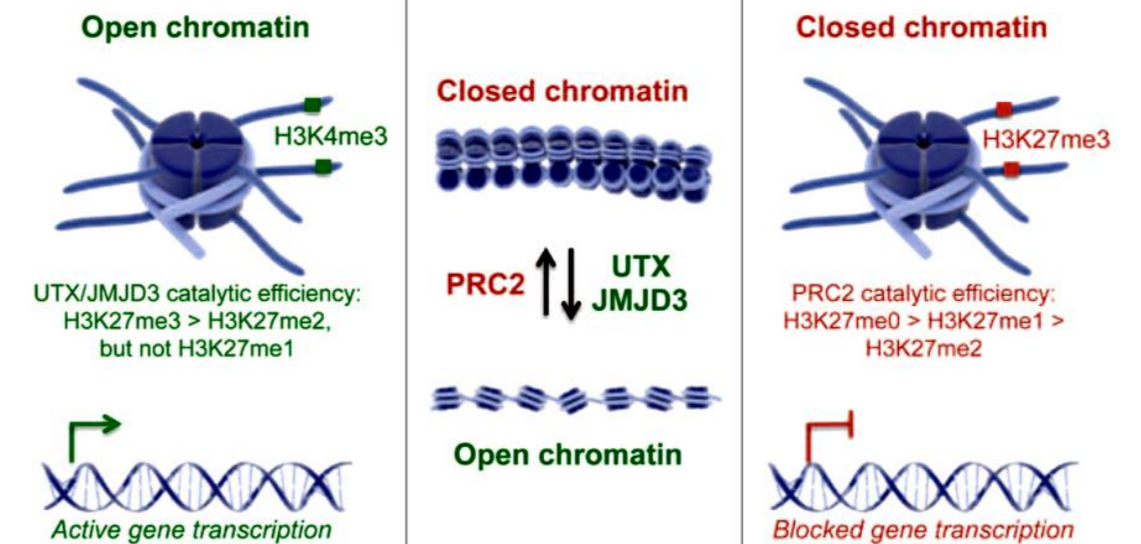
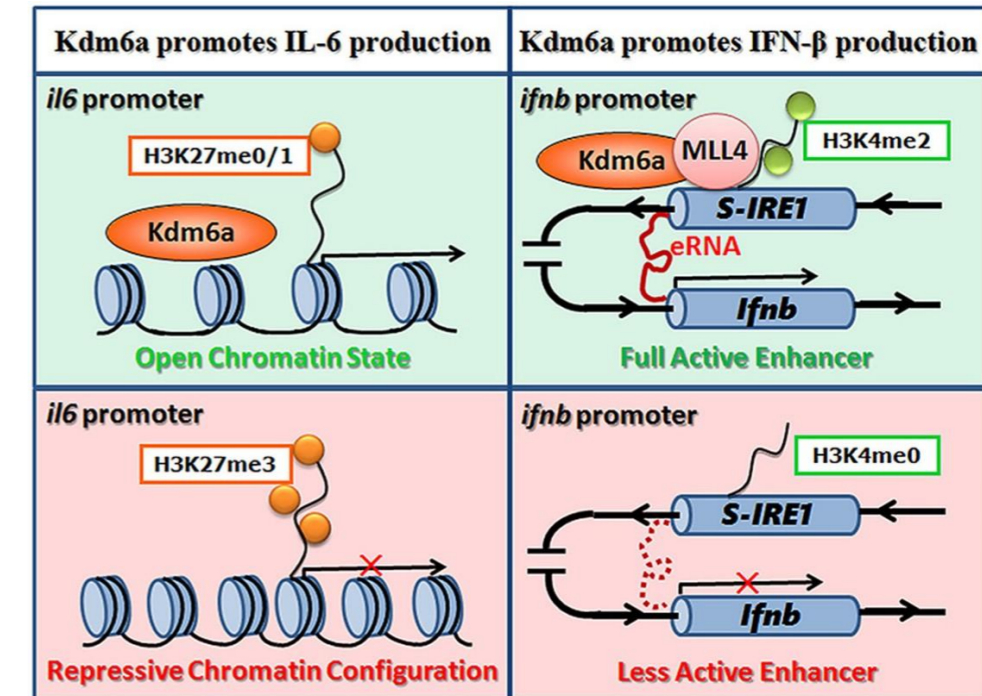
Jiaqing Yi^a, Xuanming Shi^a, Zhenyu Xuan^b, Jiang Wu^{a,*}

Demethylase Kdm6a epigenetically promotes IL-6 and IFN- β production in macrophages

Xia Li^{a,b,1}, Qian Zhang^{c,1}, Qingzhu Shi^d, Yin Liu^a, Kai Zhao^a, Qicong Shen^c, Yang Shi^d, Xingguang Liu^c, Chunmei Wang^a, Nan Li^c, Yuanfang Ma^b, Xuetao Cao^{a,c,d,*}

KDM6a

KDM5c



Methods

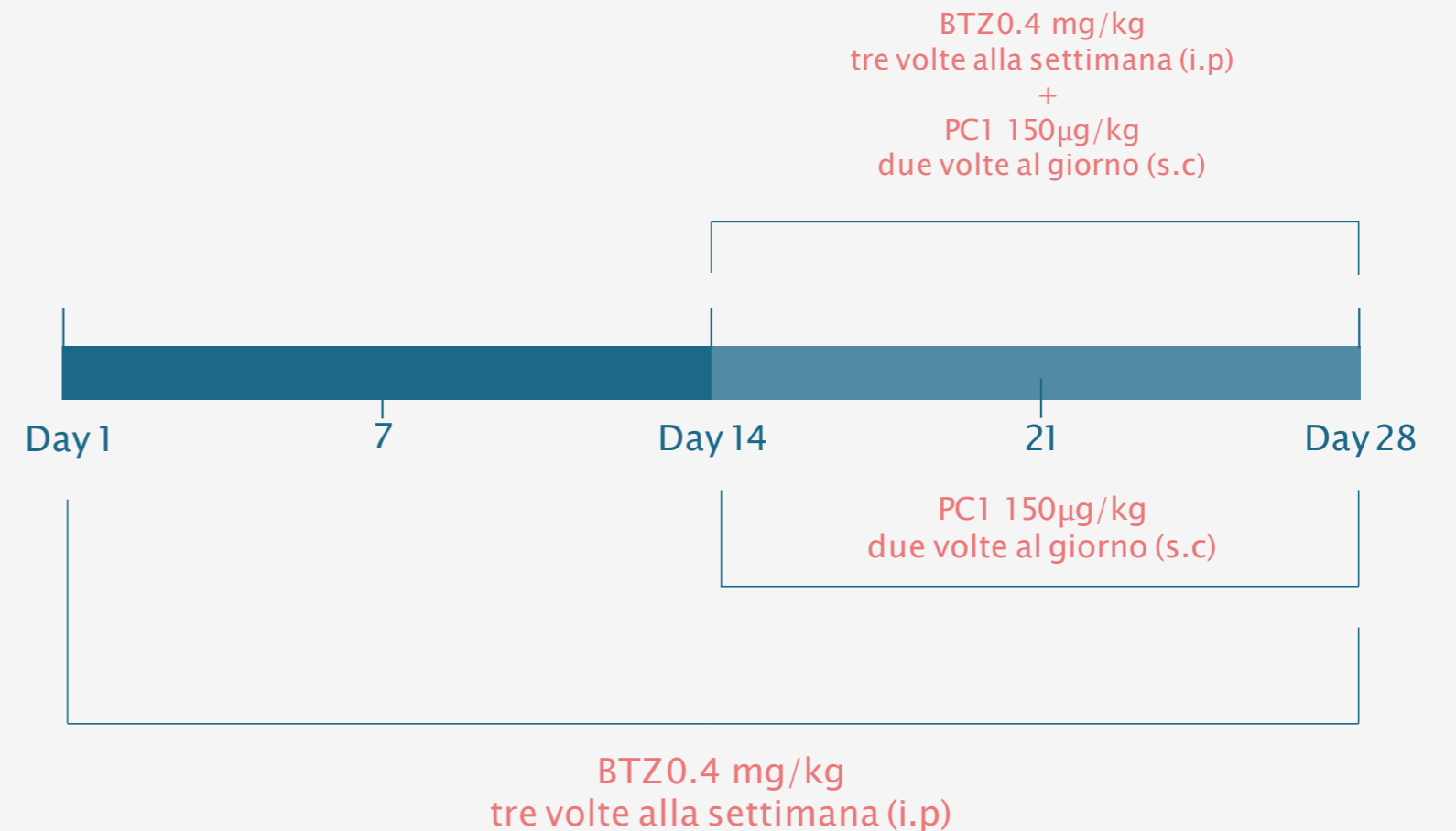
Animals



Topi maschi C57BL/ 6J
di 9 settimane suddivisi
in 6 gruppi.

Gruppi Sperimentali

CTRL T14 Soluzione salina 0,9%	BTZ T14 Bortezomib 0,4 mg/kg	CTRL T28 Soluzione salina 0,9%	BTZ T28 Bortezomib 0,4 mg/kg	BTZ+PC1 (T28) Bortezomib 0,4mg/kg + PC1 150µg/kg	PC1 PC1 150µg/kg
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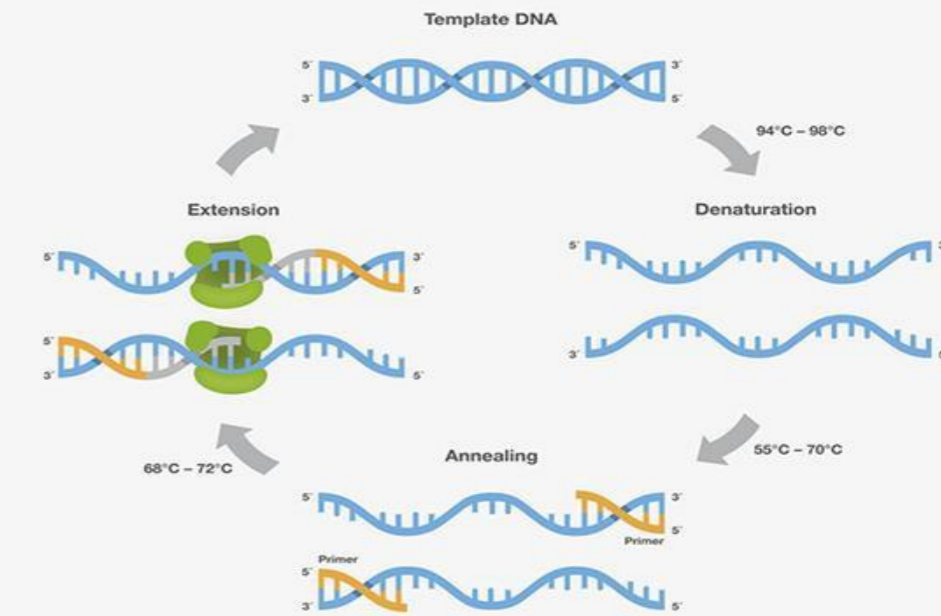
Methods



Prelievo delle aree

Analisi degli acidi nucleici :

1. Estrazione di RNA e DNA genomico
2. Valutazione quantitativa
3. Retro-trascrizione in cDNA
4. Amplificazione mediante Real-Time PCR
5. Analisi statistica

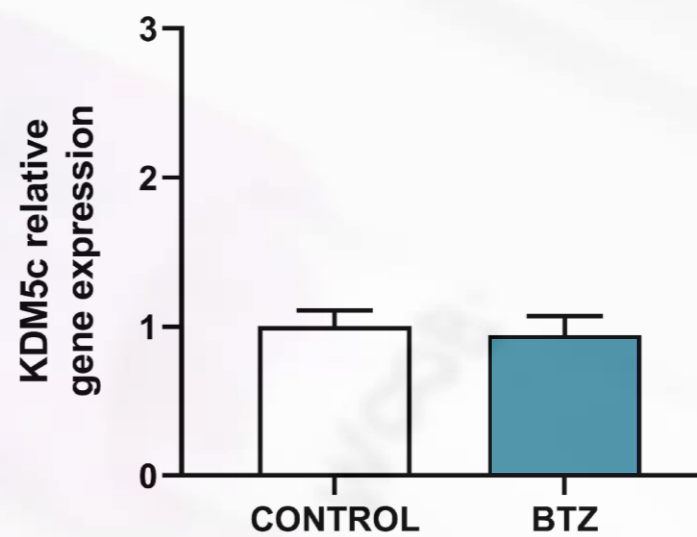
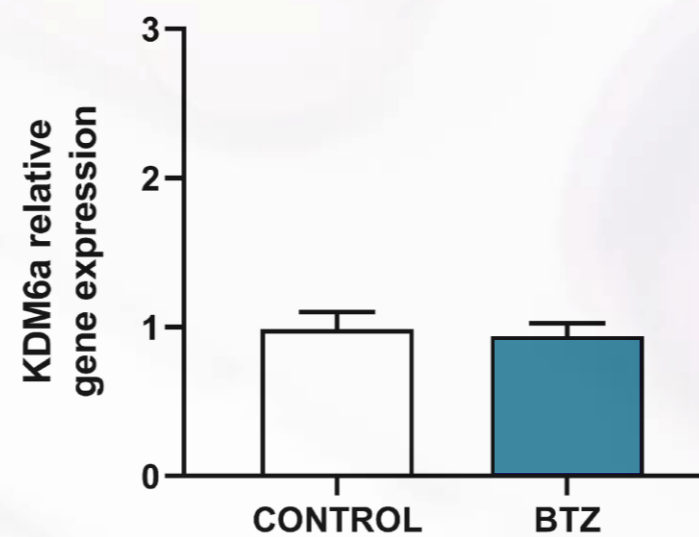
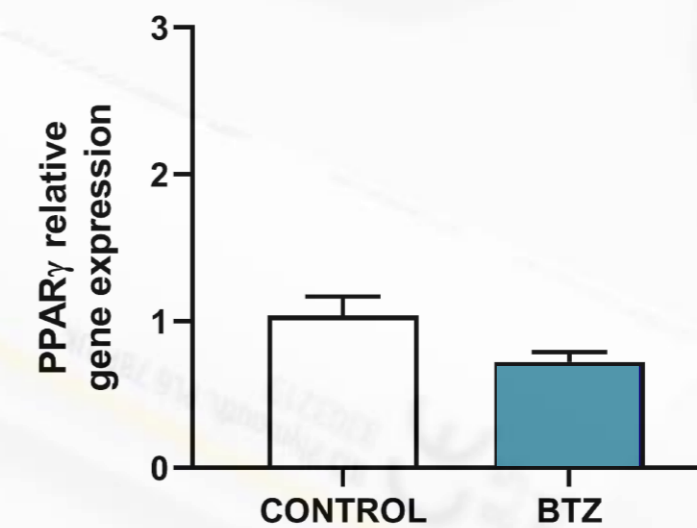
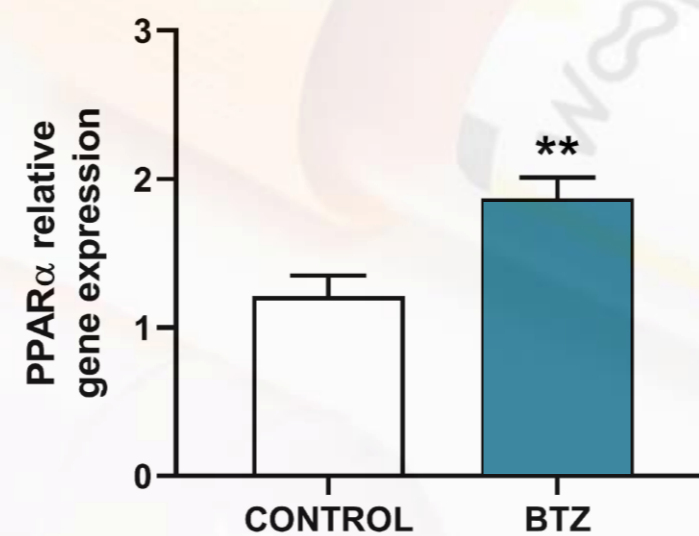


	Forward (5'-3')	Reverse (5'-3')
PPAR α	AGGTTGAGCTCAGTCAGGA	GGTCACCTACGAGTGGCATT
PPAR γ	GGAAGACCACTCGCATTCCCTT	GTAATCAGCAACCATTGGGTCA
KDM6a	TTTGGTCTACTTCCATTA	AAGCCCAAGTCGTAAATGAATTC
KDM5c	AAGATAAGACTCTGCGGAAAAAAGAT	TTGACATCCCCACCTAATTCCT
GAPDH	AACTTTGGCATTGTGGAAGG	ACACATTGGGGGTAGGAACA

Risultati

Analisi di espressione genica nei DRG dopo trattamento con BTZ per 14giorni (T14)

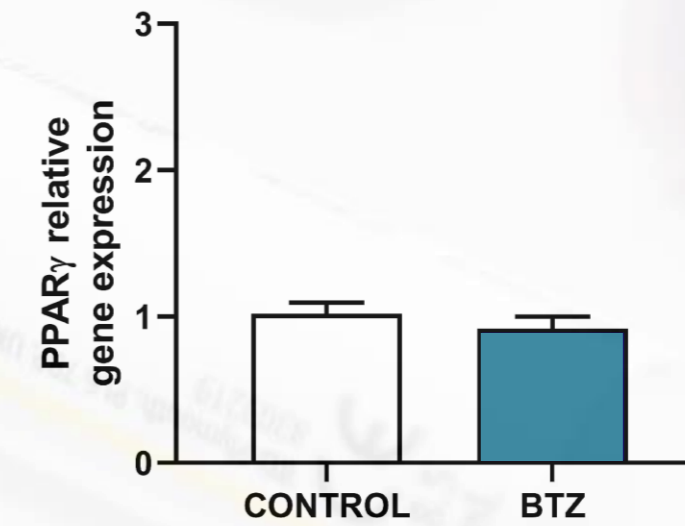
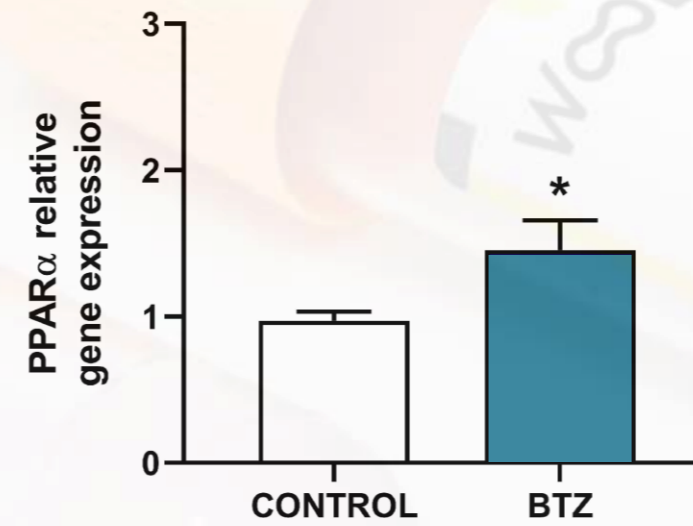
****p < 0.01 vs Control group
(Student's t-test)**



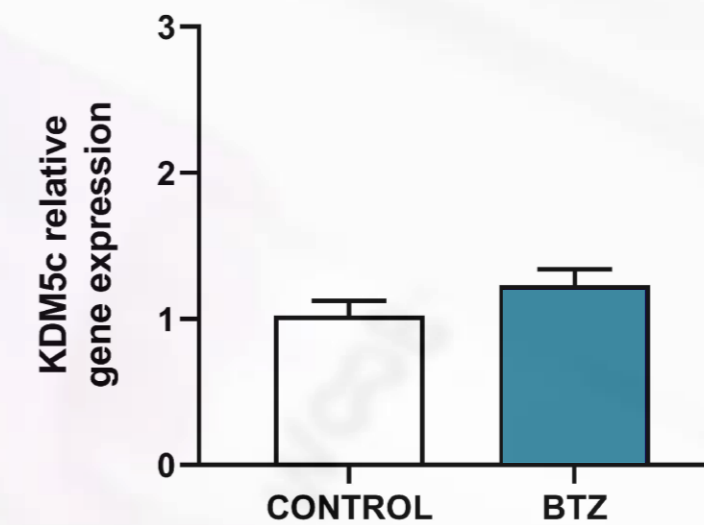
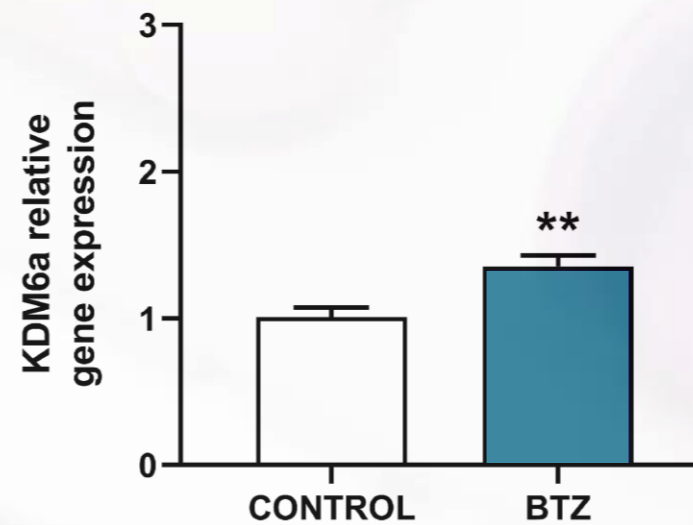
Risultati

Analisi di espressione genica nel midollo spinale dopo trattamento con BTZ per 14 giorni (T14)

* $p < 0.05$ vs Control group
(Student's t-test)



** $p < 0.01$ vs Control group
(Student's t-test)

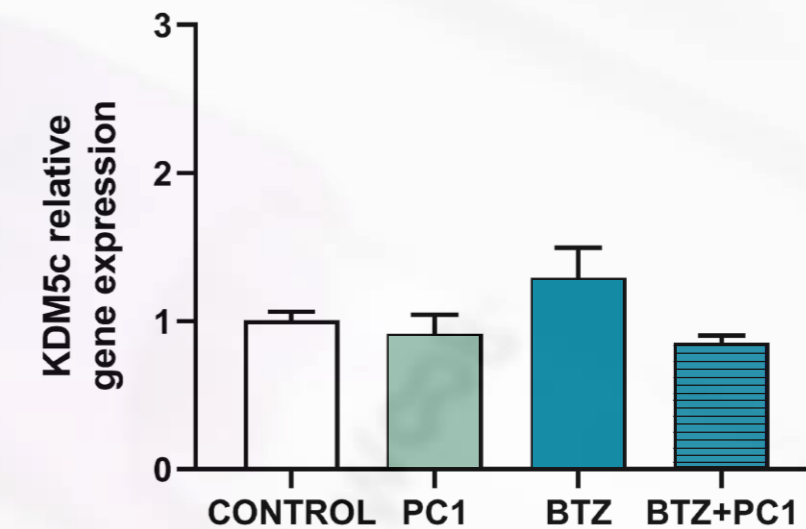
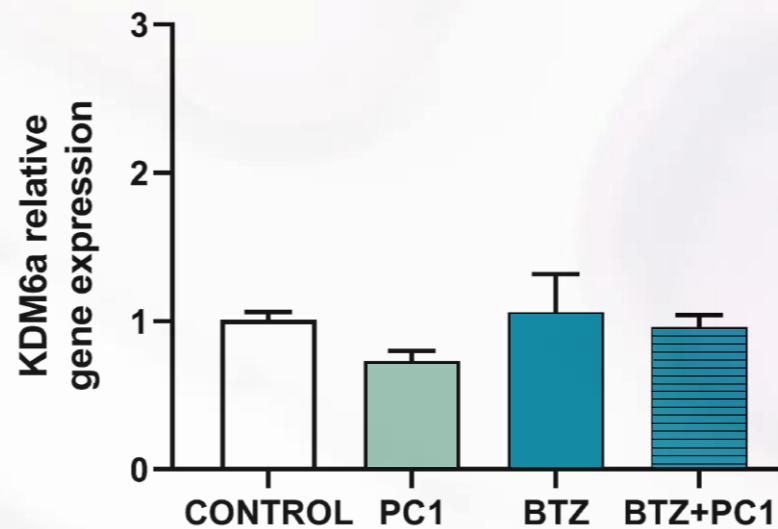
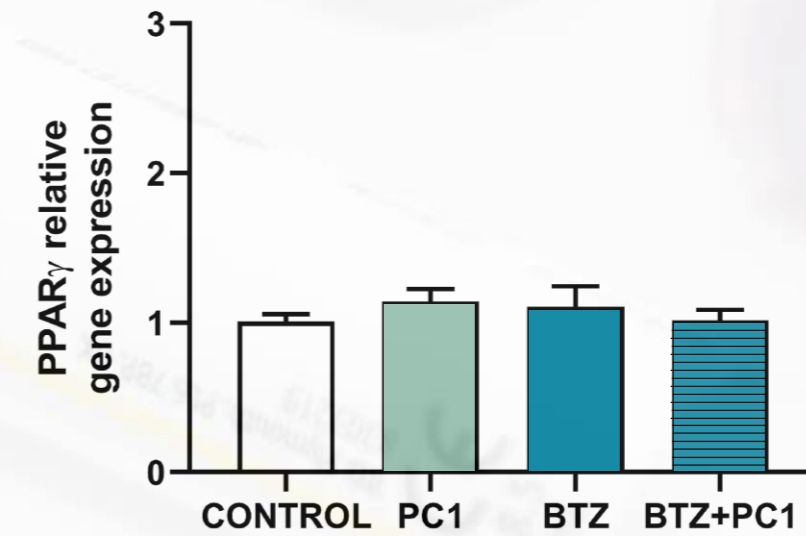
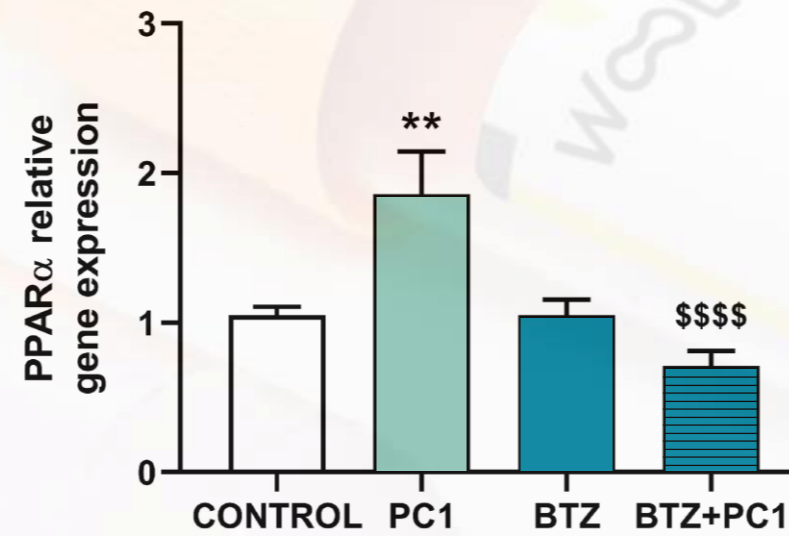


Risultati

Analisi di espressione genica nei DRG dopo trattamento con BTZ e PC1 per 28 giorni (T28)

**** $p < 0.01$ vs Control group;**
****** $p < 0.0001$ vs PC1 group**

(One-way ANOVA seguita da Tukey's multiple comparisons post-hoc test)



Risultati

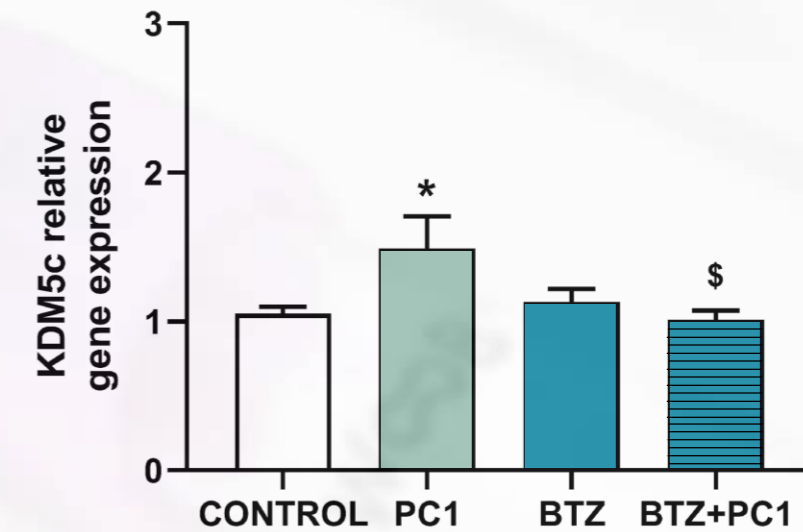
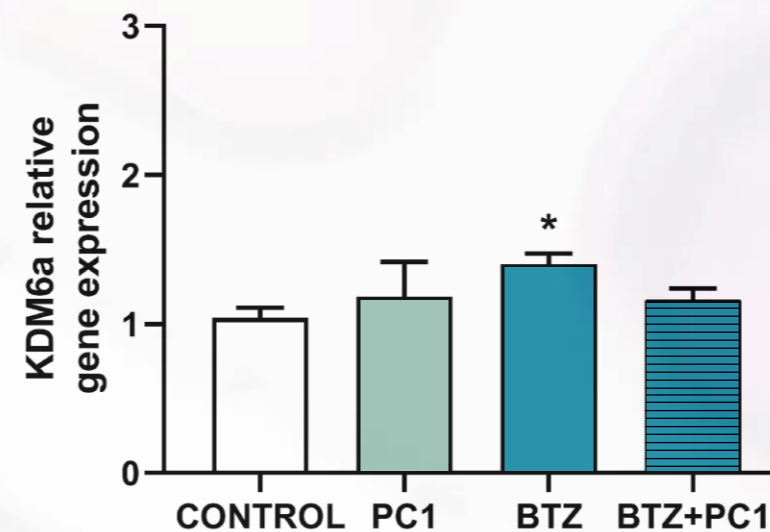
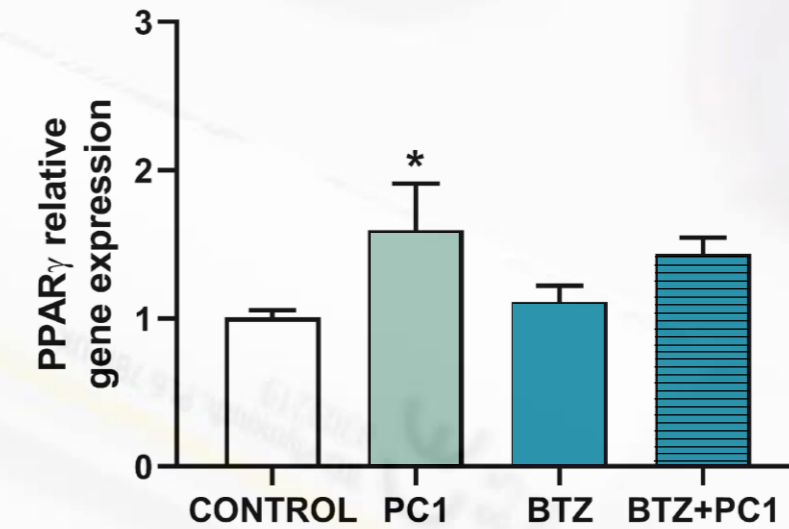
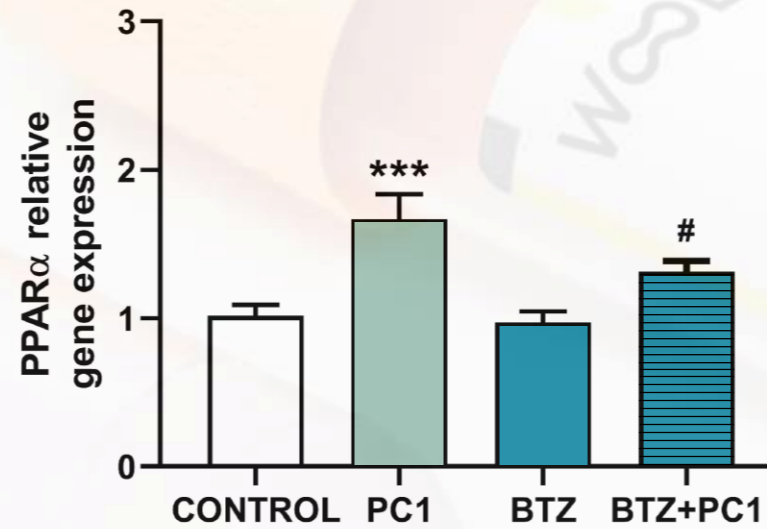
Analisi di espressione genica nel midollo spinale dopo trattamento con BTZ per 28 giorni (T28)

*** $p < 0.001$ vs Control group;
* $p < 0.05$ vs Control group;
$p < 0.05$ vs BTZ group

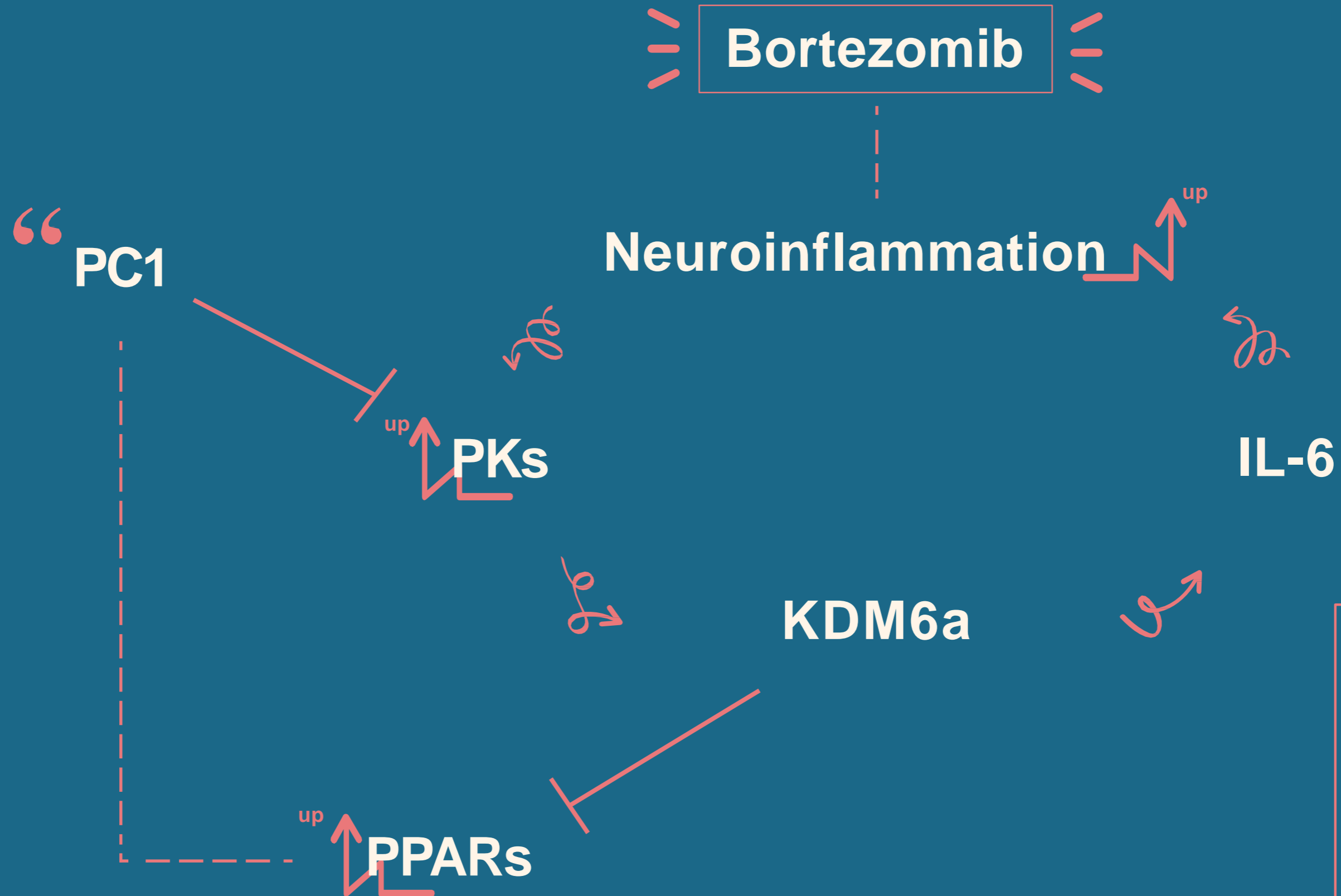
(One-way ANOVA seguita da
Tukey's multiple comparisons
post-hoc test)

* $p < 0.05$ vs Control group;
\$ $p < 0.05$ vs PC1 group

(One-way ANOVA seguita da
Tukey's multiple comparisons
post-hoc test)



💡 hypothesis



KDM6a promotes IL-6 production

