



Targeting HDAC6 to prevent or reverse chemotherapy-induced neurotoxicities

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Disclosures

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Aims



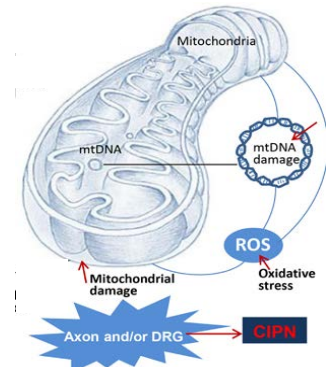
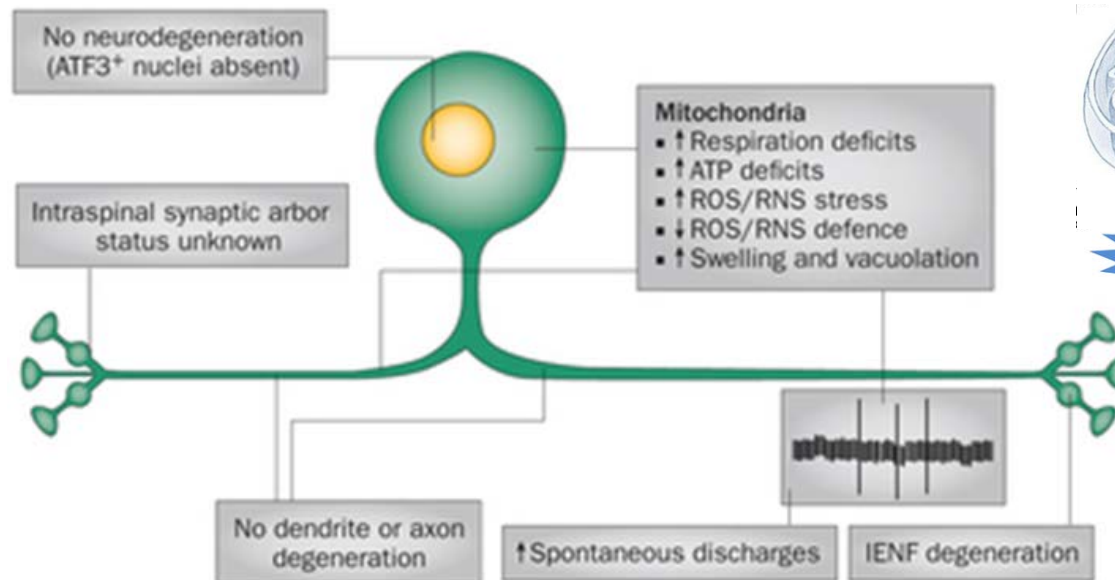
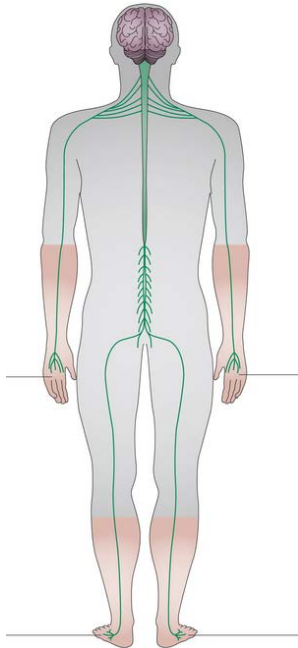
- Understanding mechanisms of onset and resolution of chemotherapy-induced peripheral neuropathy (CIPN)
- Developing novel interventions to prevent and/or reverse CIPN without interfering with cancer treatment
- Examine whether similar pathways contribute to chemobrain (Dr. Cobi Heijnen)



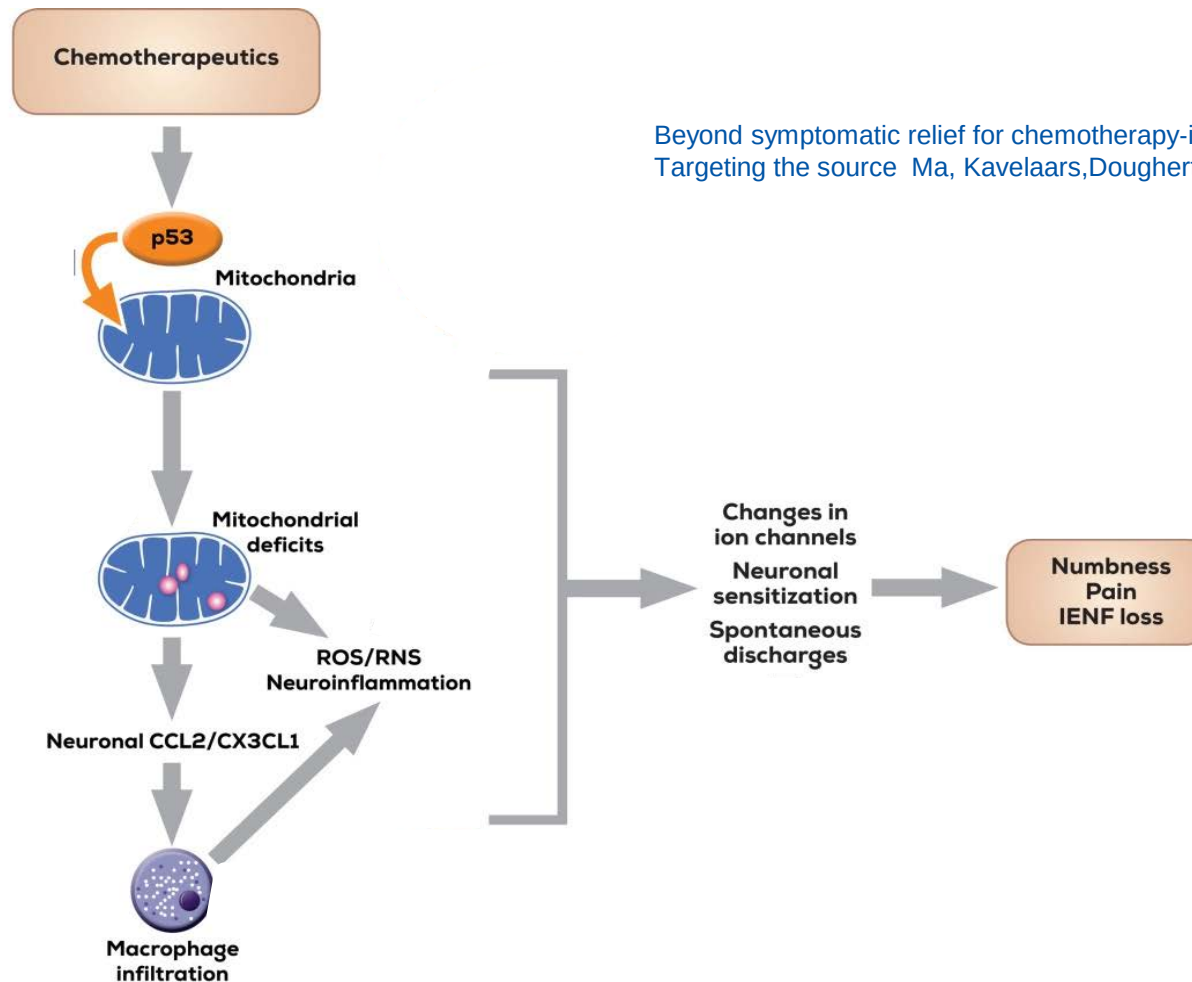


Chemotherapy-induced neuropathy

- Pain, tingling, numbness starting in hand and feet
- Dose-limiting side effect of multiple chemotherapeutics
- Does not resolve after completion of treatment in 25-30%

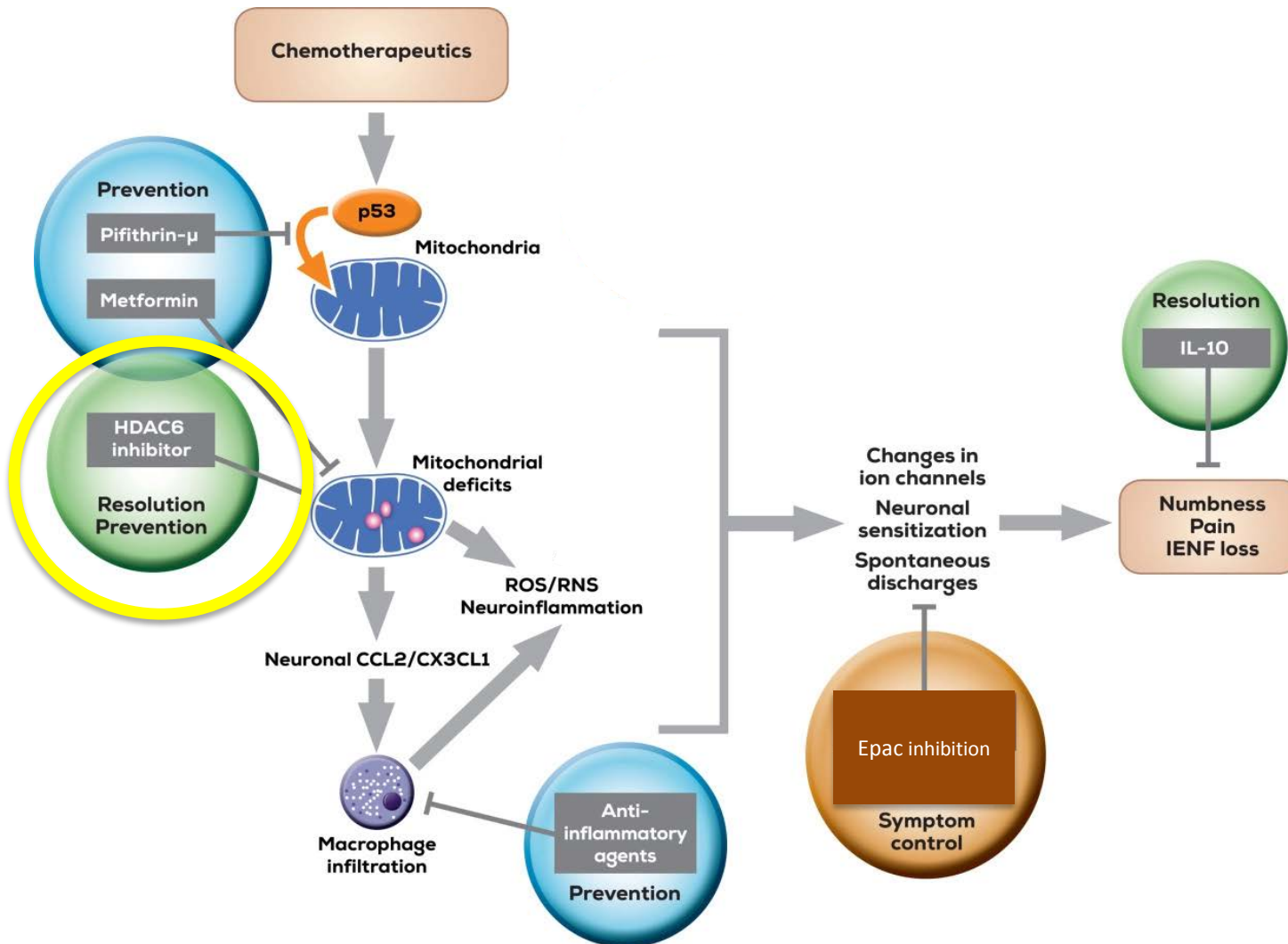


Mechanisms underlying CIPN



Beyond symptomatic relief for chemotherapy-induced peripheral neuropathy:
Targeting the source Ma, Kavelaars, Dougherty, Heijnen; Cancer 2018

Mechanisms underlying CIPN

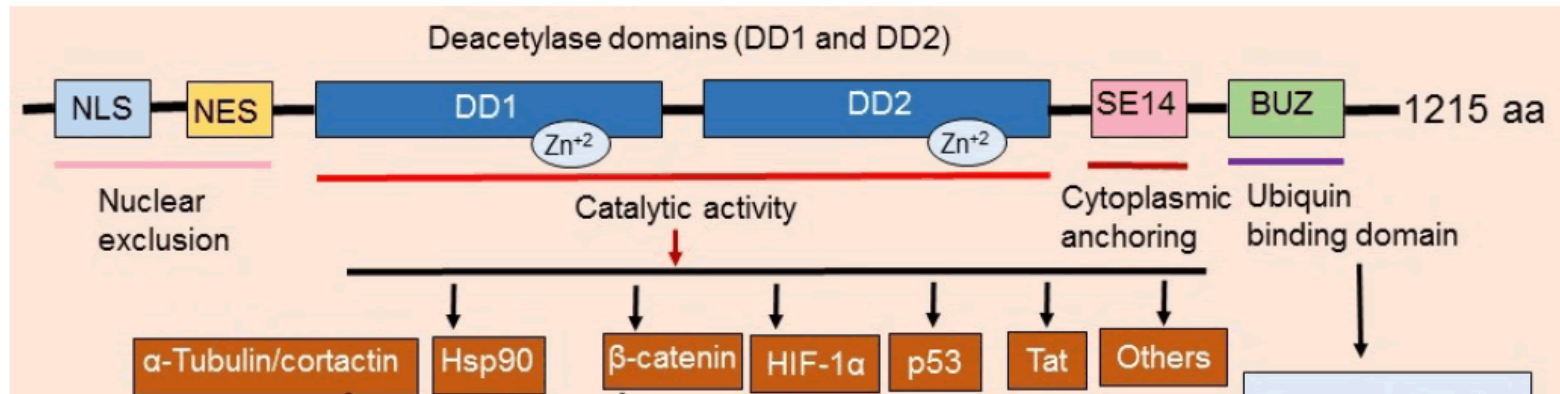


Singhmar et al. Pain, 2018
 Krukowski, Ma et al. Pain, 2017
 Maj et al. Front Mol Neurosci 2017
 Chiu et al. Cancer Res 2017
 Krukowski et al. J. Neurosci 2016
 Zhang et al. J. Pain 2016
 Zhou et al. PLoS One 2016
 Krukowski et al. Pain 2015
 Mao-Ying QL et al. PLoS One 2014

HDAC6

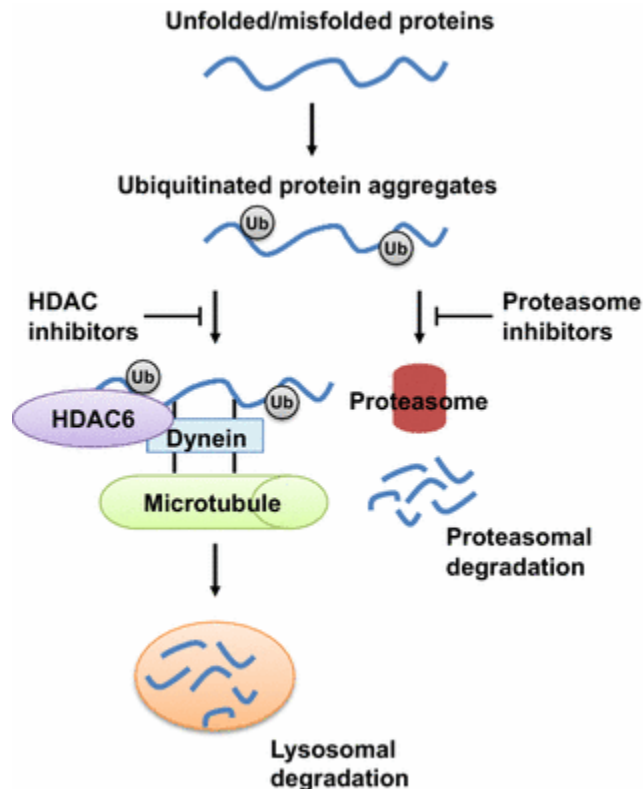
Histone deacetylase 6

Mostly cytosolic protein
Histones are NOT a major substrate

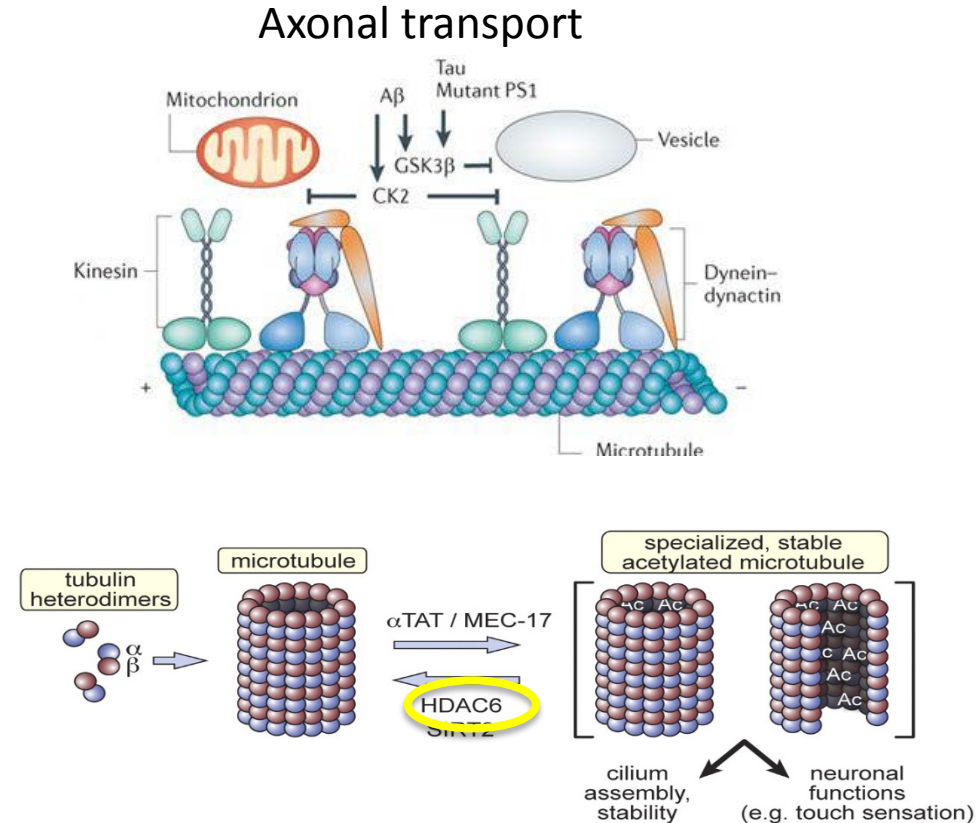


Why targeting HDAC6?

Anti-cancer effects of HDAC6 inhibitors



Pro-neuronal health effects of HDAC6 inhibitors:



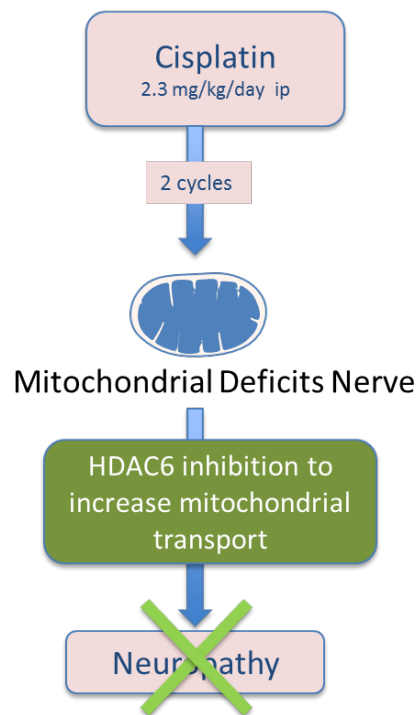


Vicky Ma

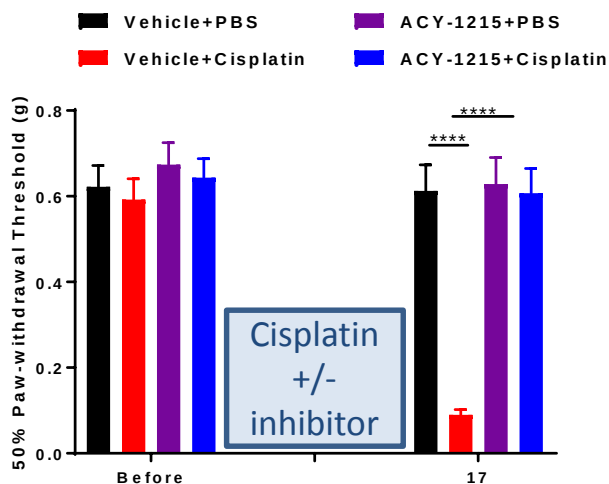
Inhibition of HDAC6 reverses neuropathic pain after cisplatin



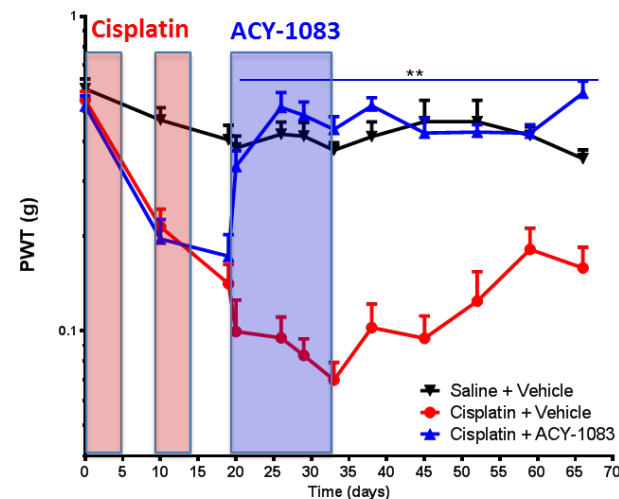
Karen Krukowski



Prevention



Reversal





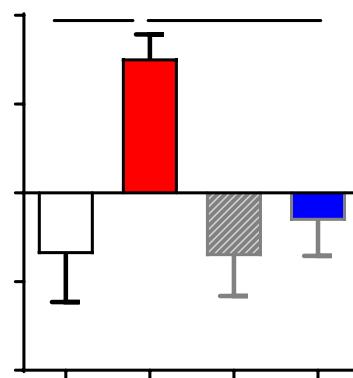
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Inhibition of HDAC6 reverses spontaneous pain after cisplatin

Conditioned place preference
Spontaneous pain



1. Train mice to associate light chamber with pain relief
2. Increase in time in light chamber indicates pain



Cisplatin
2.3 mg/kg/day ip

2 cycles



Mitochondrial Deficits Nerve

HDAC6 inhibition to
increase mitochondrial
transport

Neuropathy



Effects of HDAC6 inhibitor on numbness and innervation

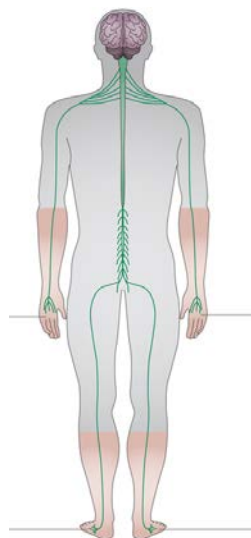
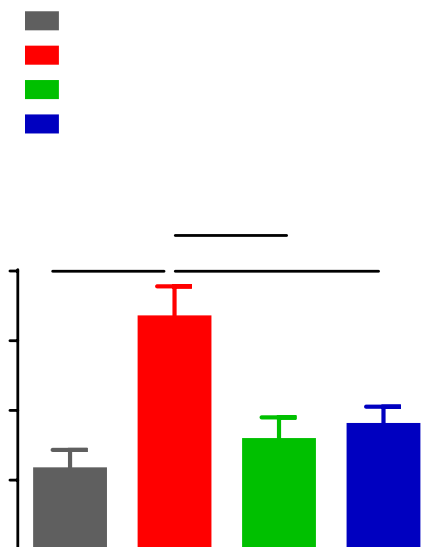


Karen Krukowski

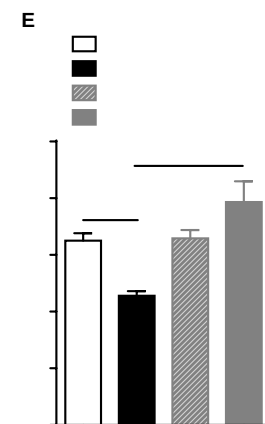
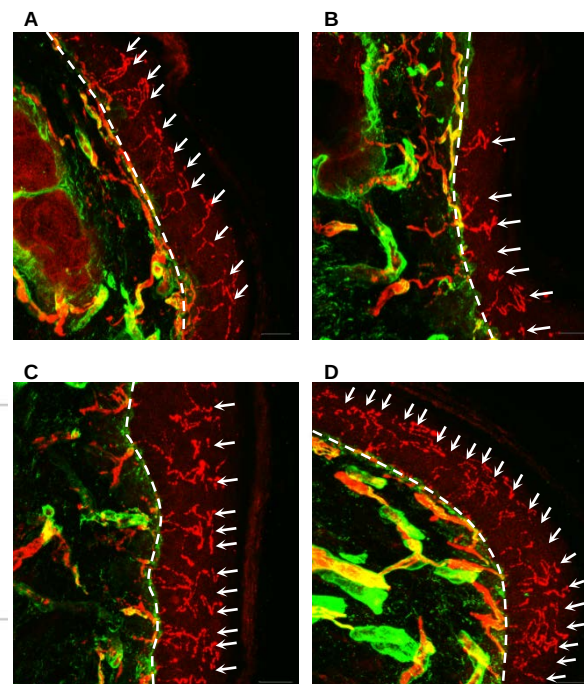
y Ma

Numbness

Detection of sticker placed on back paw



Intra-epidermal nerve fibers

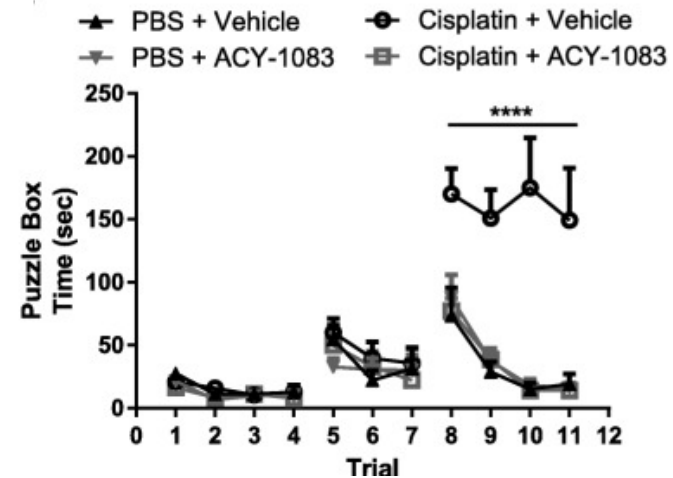




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Chemotherapy-induced cognitive deficits

2 rounds of cisplatin
12 doses of HDAC6 inhibitor
3 weeks later:
NOPRT, Y-maze, Puzzle box



Trial 1-4
Open



Trial 5-7
Bedding



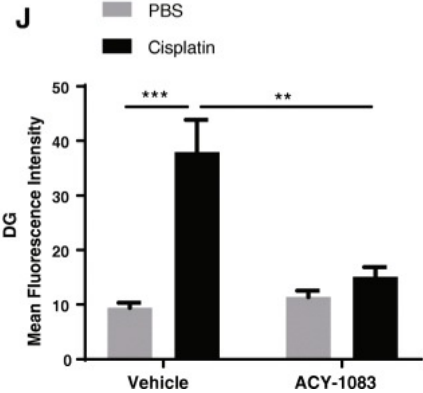
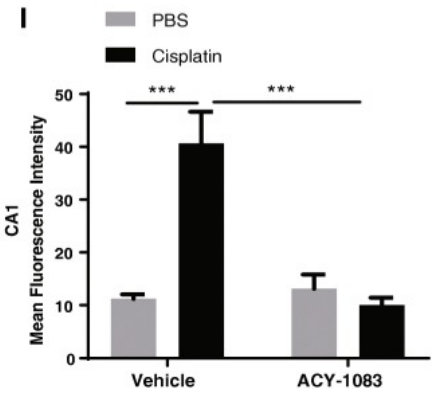
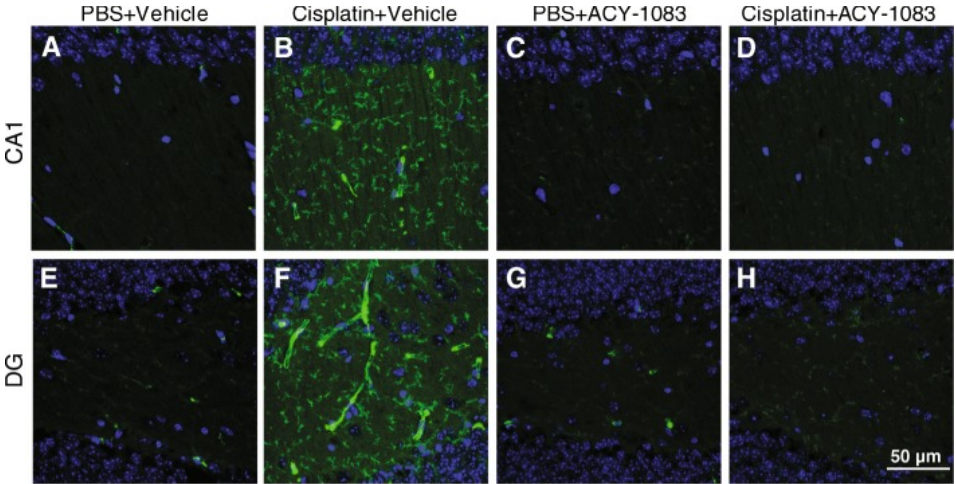
Trial 8-9
Same color lid



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HDAC6 inhibition reverses chemotherapy-induced signs of tauopathy

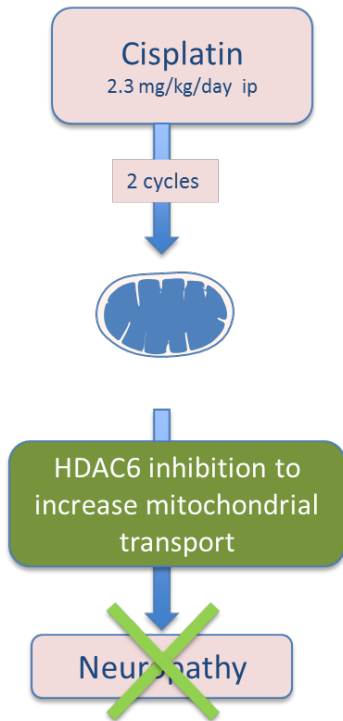
P-Tau (AT8) in hippocampus



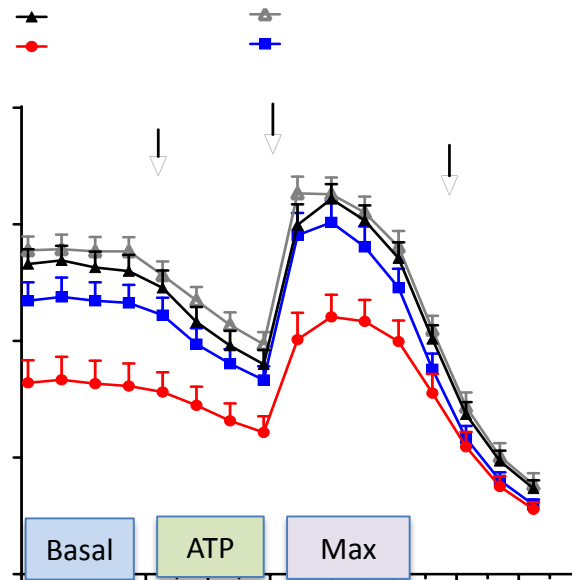


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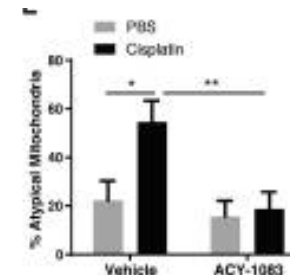
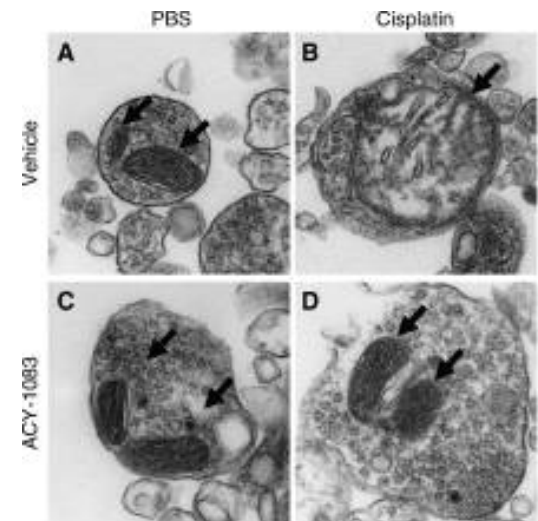
HDAC6 inhibition normalizes nerve and brain mitochondrial health



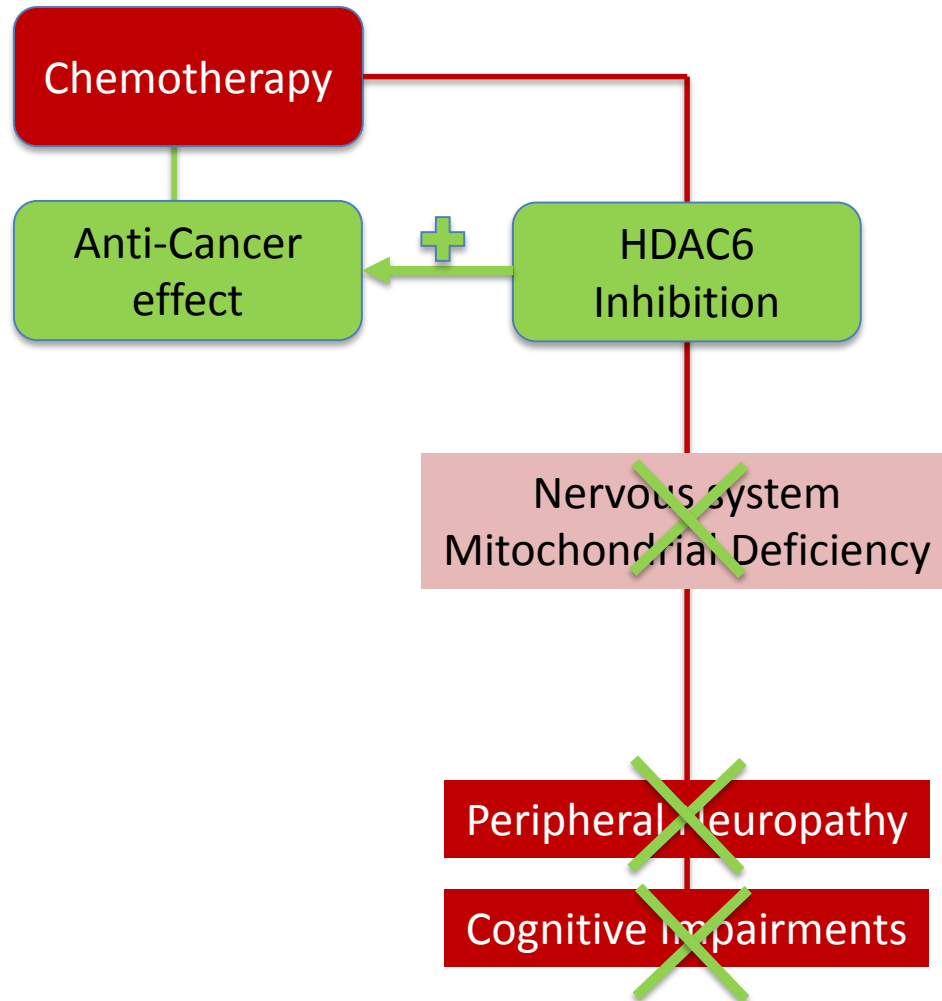
Mitochondrial function Distal Sciatic Nerve



Mitochondrial morphology Brain synaptosomes



Take Home Message



Acknowledgements

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