Targeting HDAC6 to prevent or reverse chemotherapy-induced neurotoxicities

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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%
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
Zhang et al. J. Pain 2016
Krukowski et al. Pain 2015
HDAC6
Histone deacetylase 6

 Mostly cytosolic protein
Histones are NOT a major substrate

From: Safa, AR. JPET Res 2018
Why targeting HDAC6?

Anti-cancer effects of HDAC6 inhibitors

Pro-neuronal health effects of HDAC6 inhibitors:

Axonal transport

From Int J Hematol 2016 104:300

Adapted from Leroux MR, PNAS 2010
Inhibition of HDAC6 reverses neuropathic pain after cisplatin.

Cisplatin 2.3 mg/kg/day ip

2 cycles

Mitochondrial Deficits Nerve

HDAC6 inhibition to increase mitochondrial transport

Pain

Krukowski, Ma et al. Pain, 2016; Ma et al. 2018 in prep
Inhibition of HDAC6 reverses spontaneous pain after cisplatin

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

Conditioned place preference
Spontaneous pain

Cisplatin
2.3 mg/kg/day ip
2 cycles
Mitochondrial Deficits Nerve
HDAC6 inhibition to increase mitochondrial transport
Neuropathy

Pain

Krukowski, Ma et al. Pain, 2016; Ma et al. 2018 in prep

Vicky Ma
Effects of HDAC6 inhibitor on numbness and innervation

Numbness

Detection of sticker placed on back paw

Intra-epidermal nerve fibers

Krukowski, Ma et al. Pain, 2016; Ma et al. 2018 in prep
Chemotherapy-induced cognitive deficits

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

Ma et al. Acta Neuropath Comm 2018
HDAC6 inhibition reverses chemotherapy-induced signs of tauopathy

P-Tau (AT8) in hippocampus

Ma et al. Acta Neuropath Comm 2018
HDAC6 inhibition normalizes nerve and brain mitochondrial health

Mitochondrial function
Distal Sciatic Nerve

Mitochondrial morphology
Brain synaptosomes

Cisplatin
2.3 mg/kg/day ip

2 cycles

HDAC6 inhibition to increase mitochondrial transport

HDAC6 inhibition to increase mitochondrial transport

Krukowski, Ma et al. Pain, 2016; Ma et al. Acta Neuropath Comm 2018
Take Home Message

Chemotherapy

Anti-Cancer effect

HDAC6 Inhibition

Nervous system Mitochondrial Deficiency

Peripheral Neuropathy

Cognitive Impairments
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