



2019

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Enteric nervous system toxicity underlying gastrointestinal side-effects of chemotherapy: mechanisms and potential treatments

MASCC/ISOO

Annual Meeting on Supportive Care in Cancer

www.mascc.org/meeting

Follow us on Twitter: @CancerCareMASCC



MASCC
Multinational Association
of Supportive Care in Cancer

ISOO
International Society
on Oncology Supportive Care

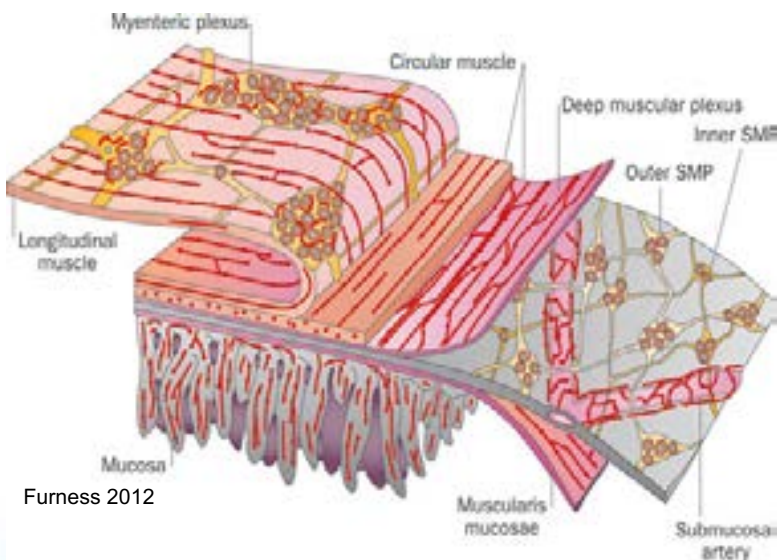


#MASCC19

Drug	Neurotoxic Complications	
	Central Nervous System	Peripheral Nervous System
Cisplatin	Encephalopathy, headache, stroke, seizures	Sensory peripheral neuropathy Lhermitte's sign, muscle cramps, <u>nausea, vomiting, diarrhoea</u>
Carboplatin	Cortical blindness	Sensory peripheral neuropathy, stomach cramps, <u>constipation, diarrhoea and vomiting</u>
Oxaliplatin	No adverse effects	Post-infusion parasthesia, sensory peripheral neuropathy, <u>constipation, diarrhoea, nausea, vomiting</u>
5-Fluorouracil	Cerebellar dysfunction, inflammatory leukoencephalopathy	<u>Nausea, vomiting, diarrhoea, constipation</u> Rare: peripheral neuropathy
Irinotecan	Rare: dysarthria, ataxia of the arms and legs	<u>Diarrhoea, stomach cramps, nausea, vomiting, constipation</u>



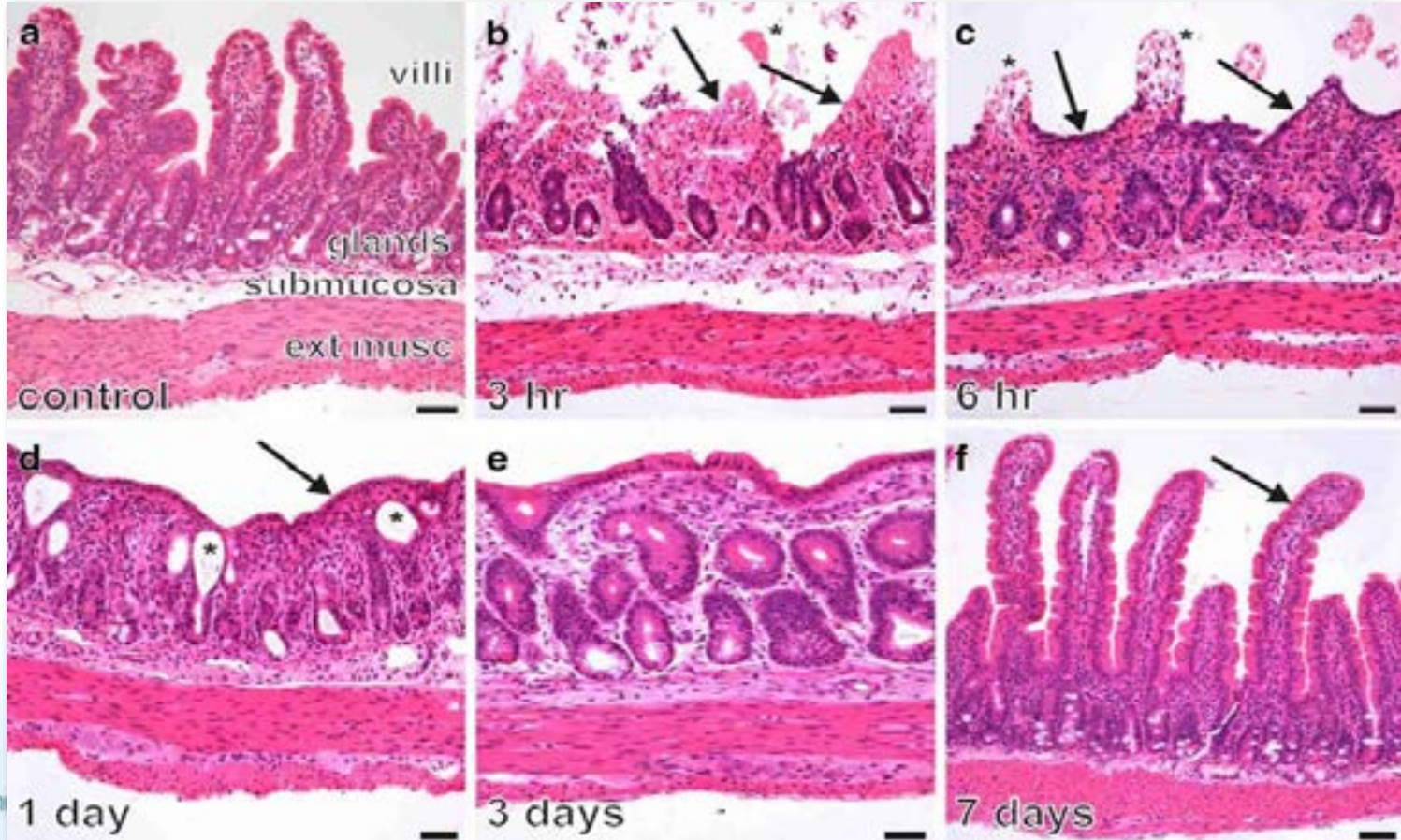
Enteric Nervous System



- Enteric nervous system (ENS) controls all GI functions
- The number of enteric neurons in a human is estimated to be 200-600 million ~ the same as in the spinal cord.
- Coordinated gut motility persists even in the total absence of connections between the gut and the CNS.



Main concept



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Human studies: fresh colon specimens from non-obstructive carcinoma patients

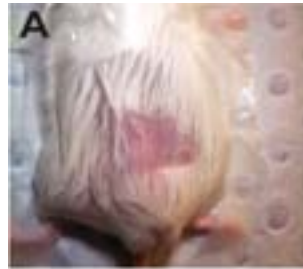
Animal models:

Chemotherapy



The Multinational Cancer

Colorectal cancer



Animal anaesthetised and prepared for surgery



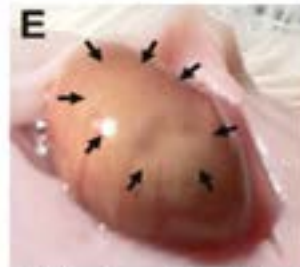
Abdominal incision



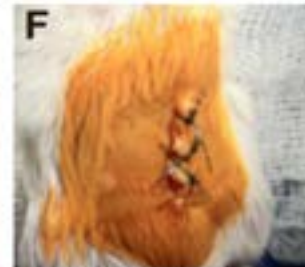
Exteriorisation of the caecum



Injection of C26 colorectal cancer cells



Bulla formation in the wall of the caecum



Abdominal suture



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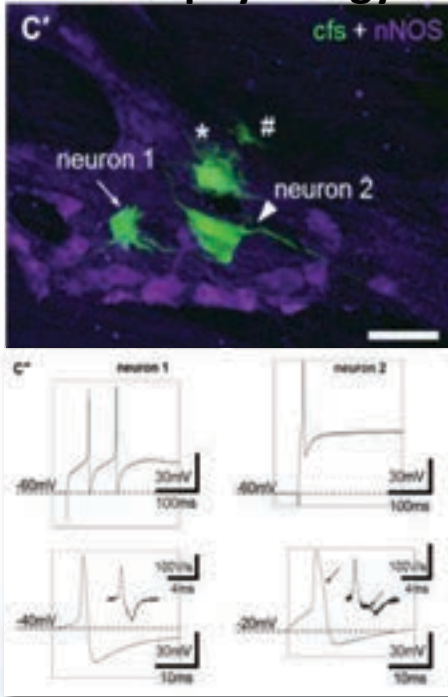
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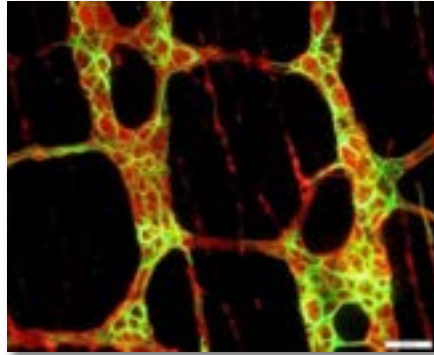


Methods

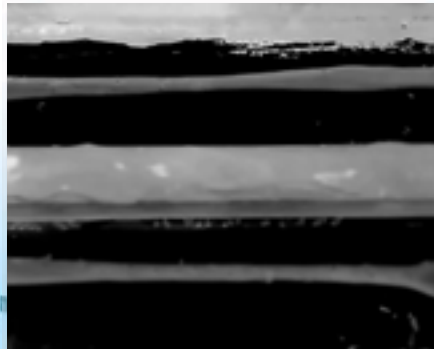
Electrophysiology



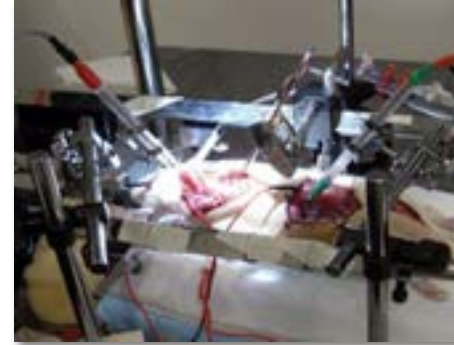
Immunohistochemistry Confocal microscopy Molecular biology



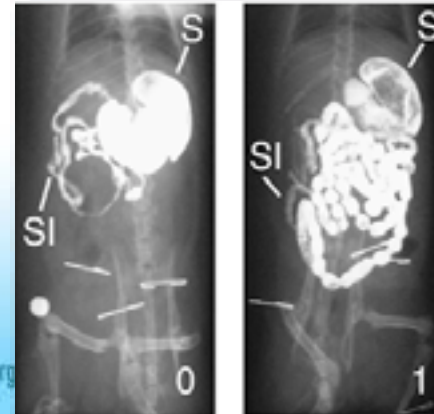
Motility



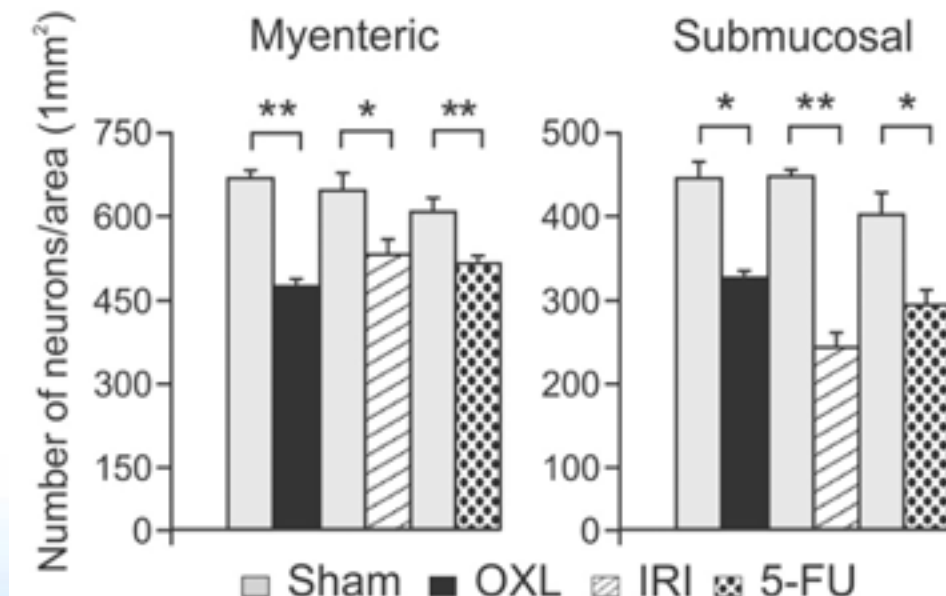
In vivo nerve recording



Small animal *in vivo* X-ray



Chemotherapy-induced loss of enteric neurons



Side-effects of oxaliplatin treatment: mouse model

Chronic *in vivo* Oxaliplatin treatment causes:

- loss of body weight
- severe constipation
- decrease in food intake
- increase in kaolin consumption (pica
– equivalent to nausea and vomiting in humans)

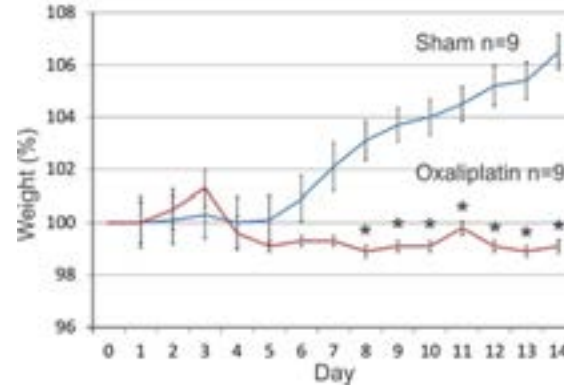
Excised colons



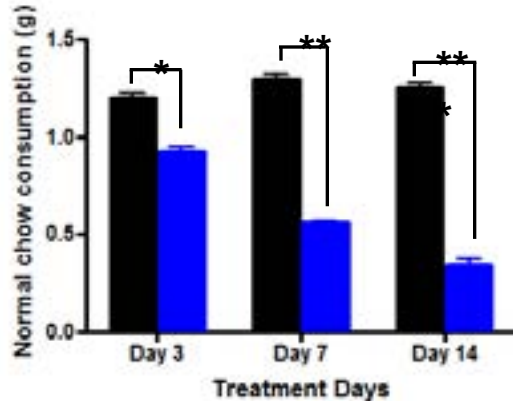
Sham Oxaliplatin

The Multinational Association of Supportive Care

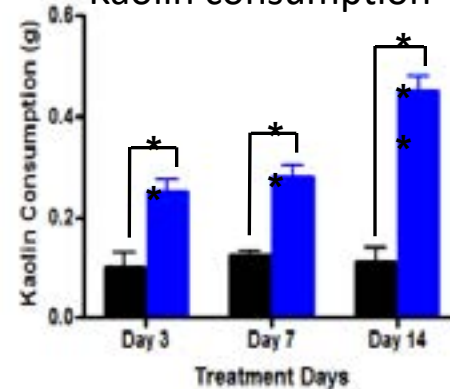
Effect of *in vivo* treatment with Oxaliplatin
on animal body weight



Normal chow consumption



Kaolin consumption



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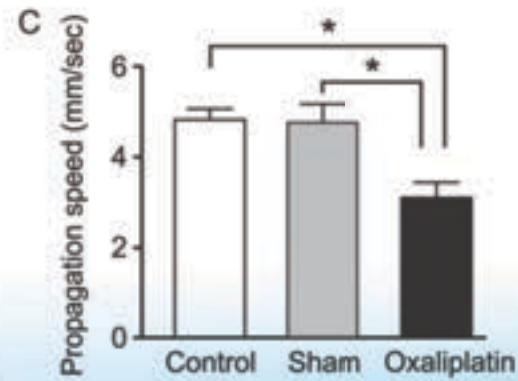
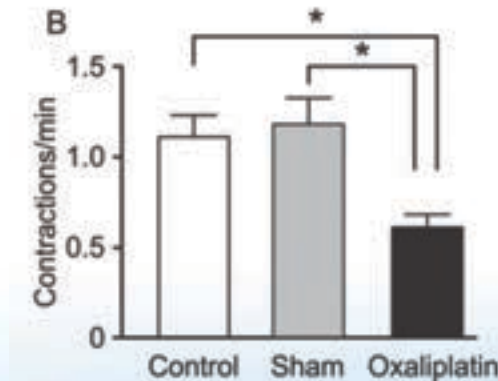
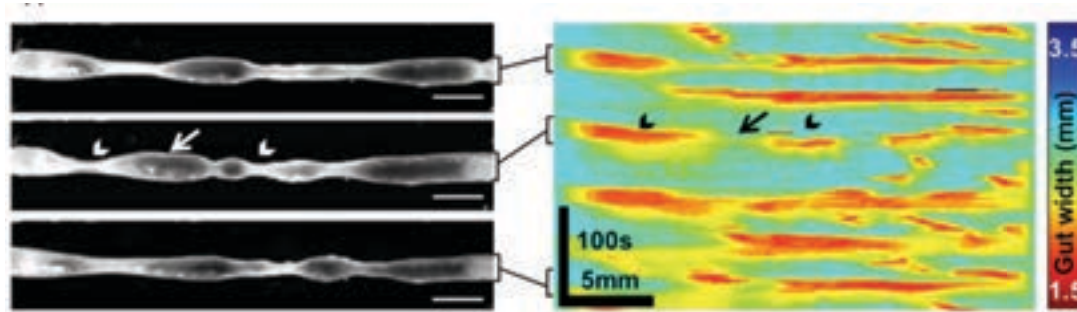
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Oxaliplatin-induced gastrointestinal dysfunctions

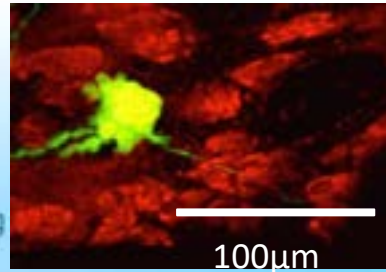
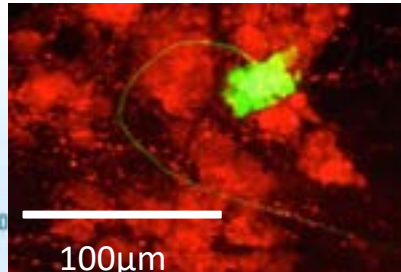
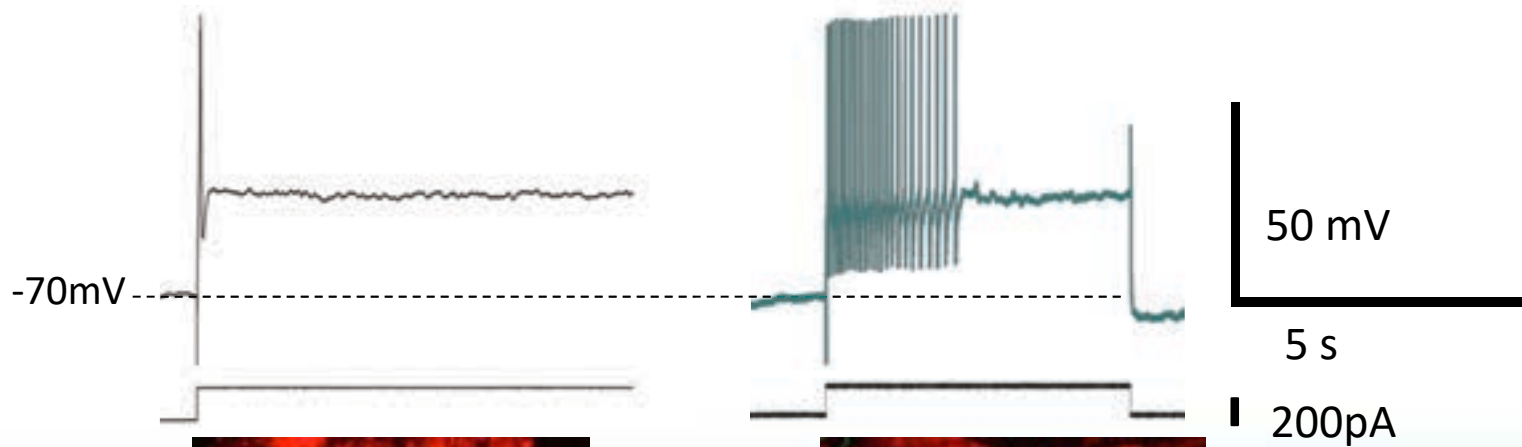


McQuade et al 2016

Hyperexcitability of colonic myenteric neurons from chemotherapy-treated patients

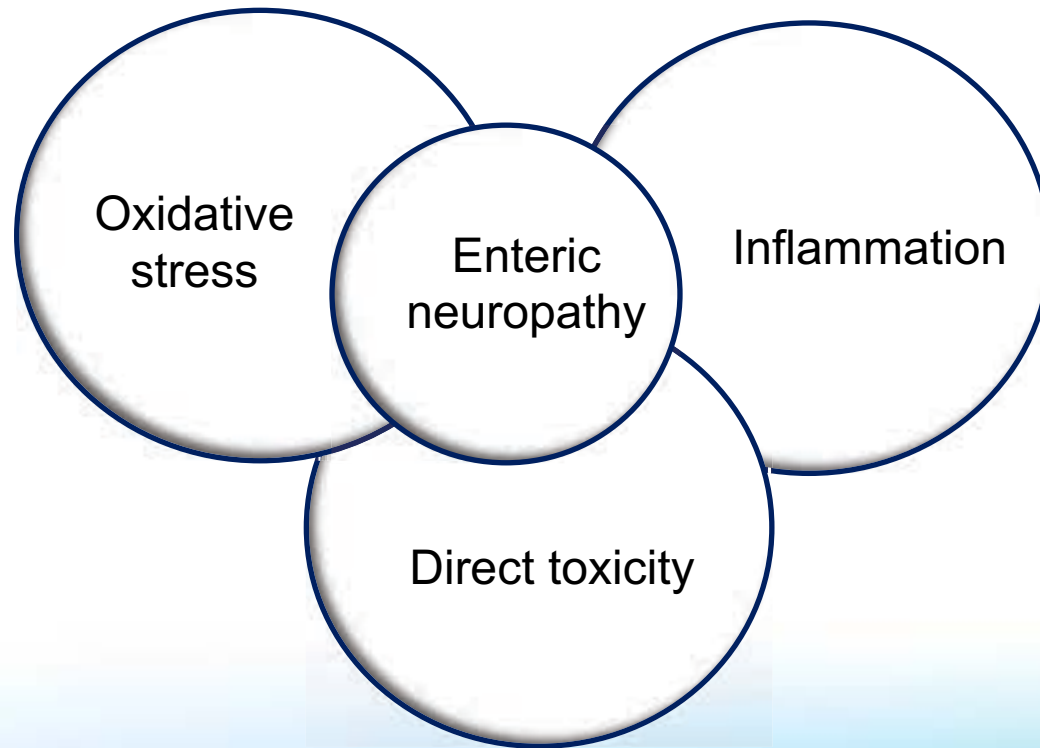
Untreated

Chemotherapy-treated

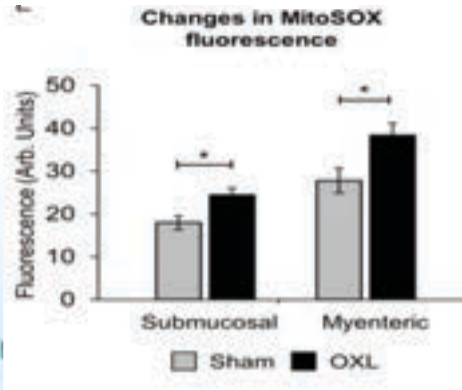
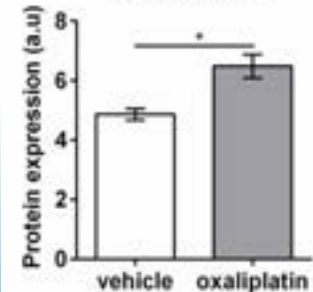
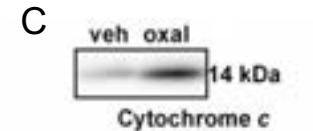
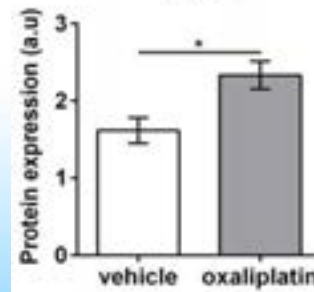
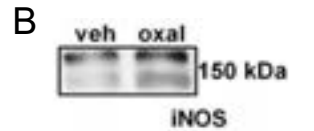
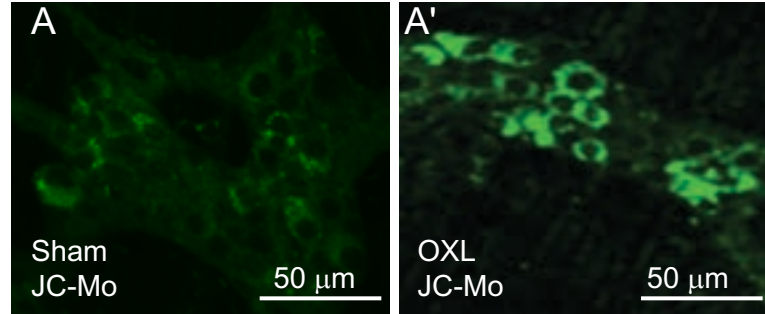
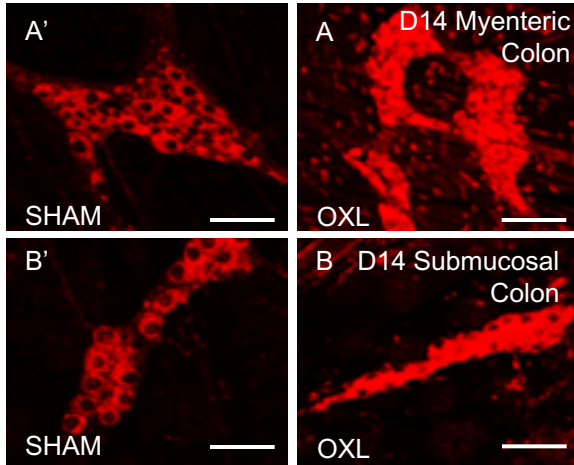


Carbone S et al., NGM
2016, 28(7):975-84



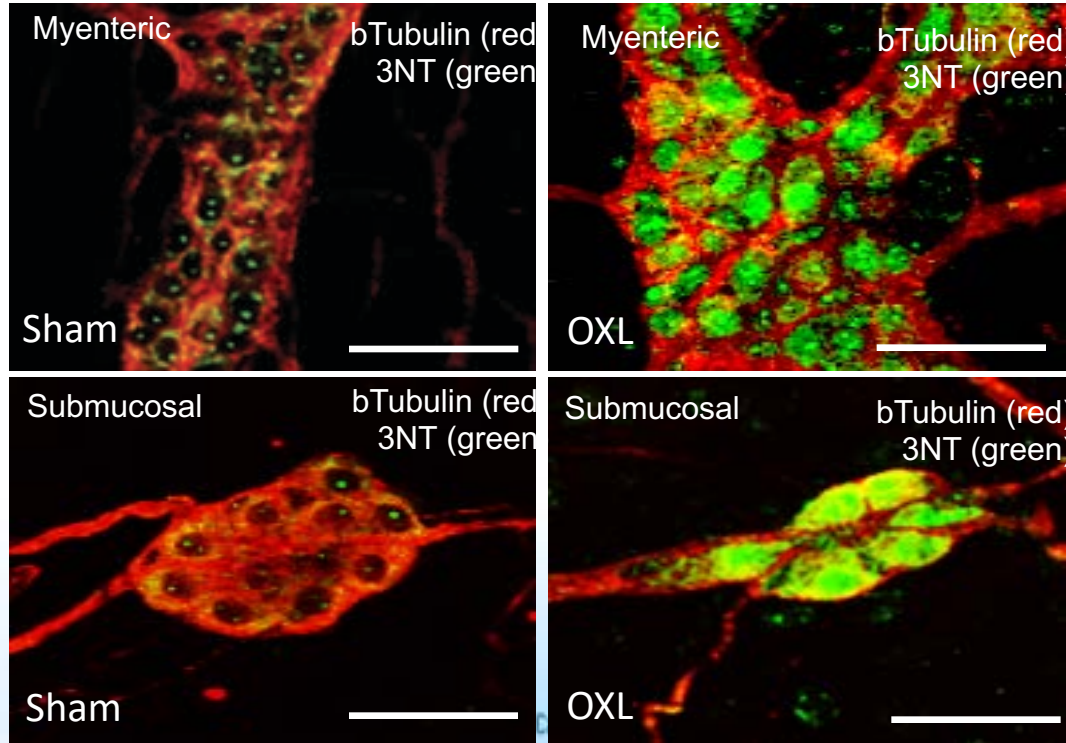


Oxaliplatin-induced oxidative stress

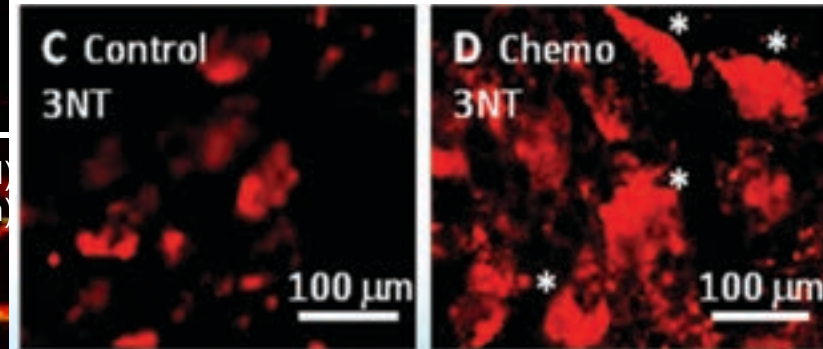


Aggregates of nitrosylated proteins in enteric neurons

Mouse



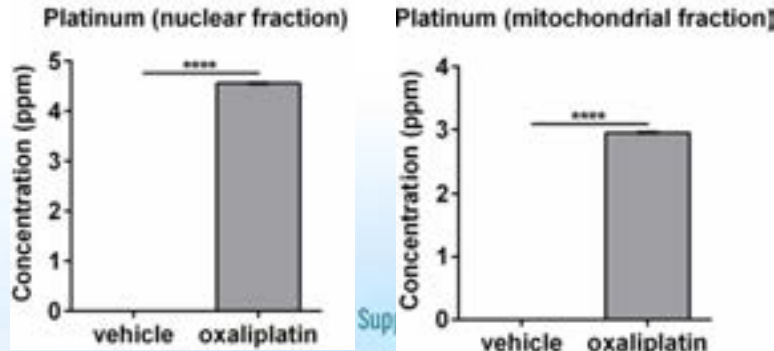
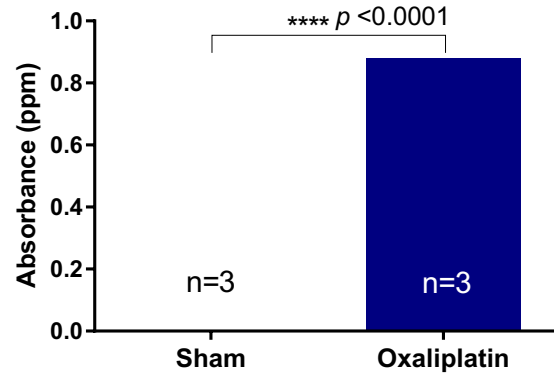
Human



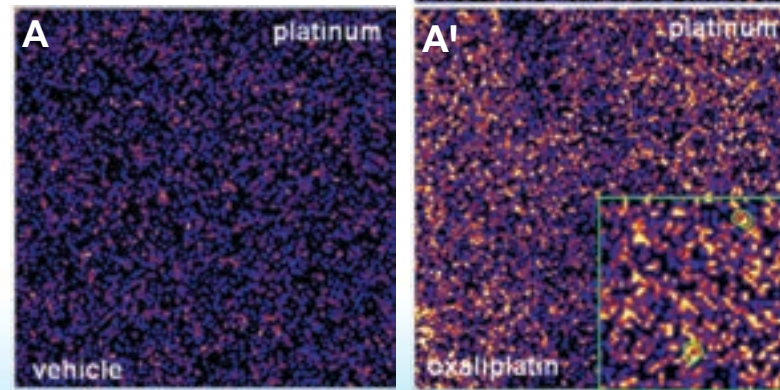
McQuade et al 2016
*BrJPharmacol*173(24):3502-21

Ex vivo platinum detection in enteric neurons using atomic absorption spectrophotometry

Platinum absorbance following
in vivo oxaliplatin administration

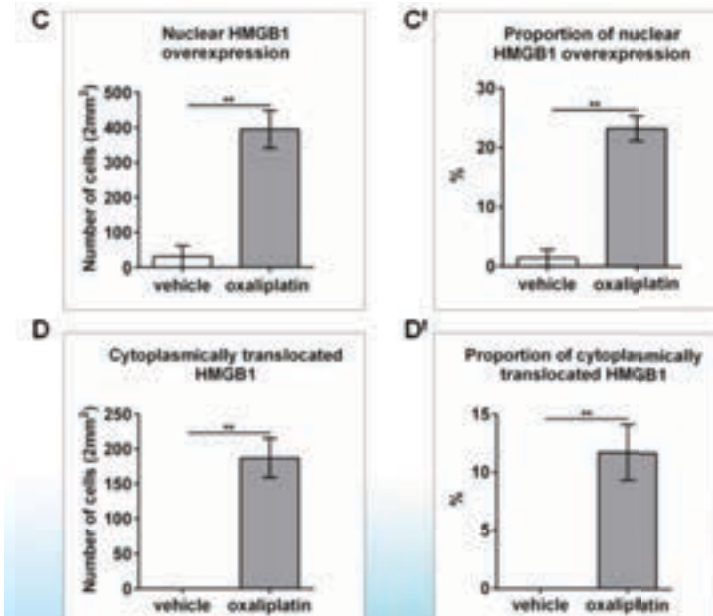
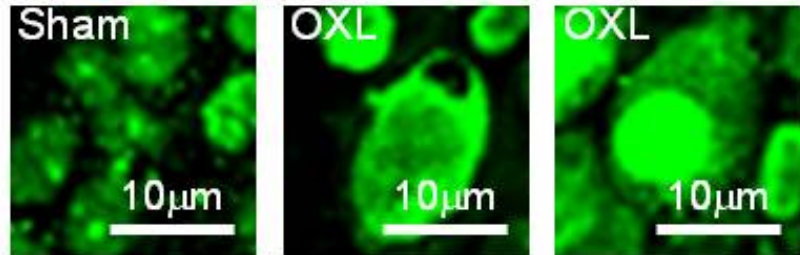
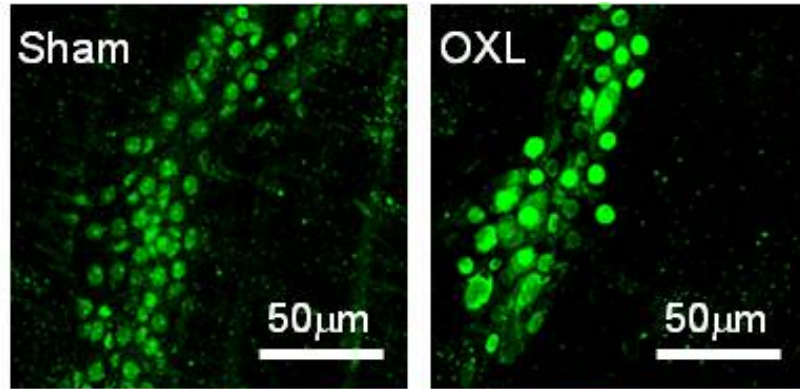


Pt in enteric neurons XFM (Synchrotron)



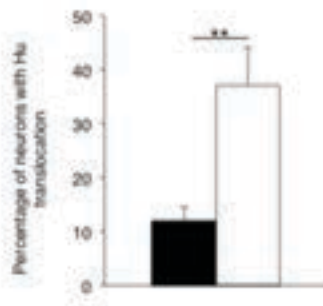
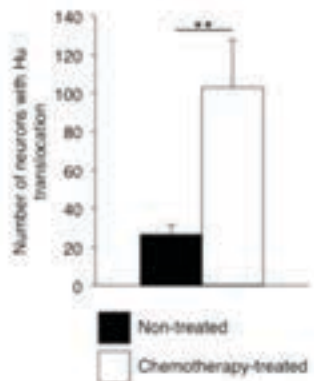
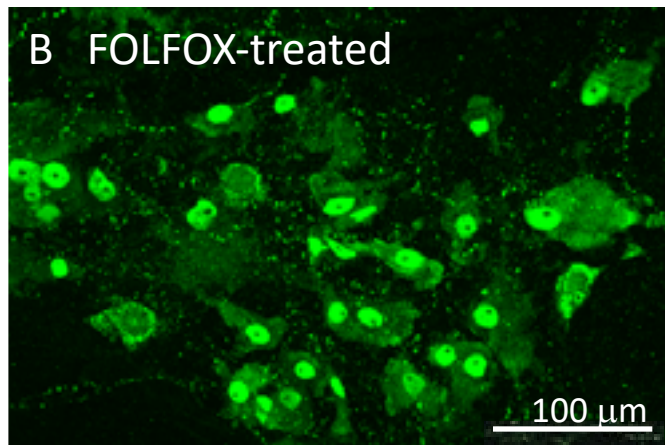
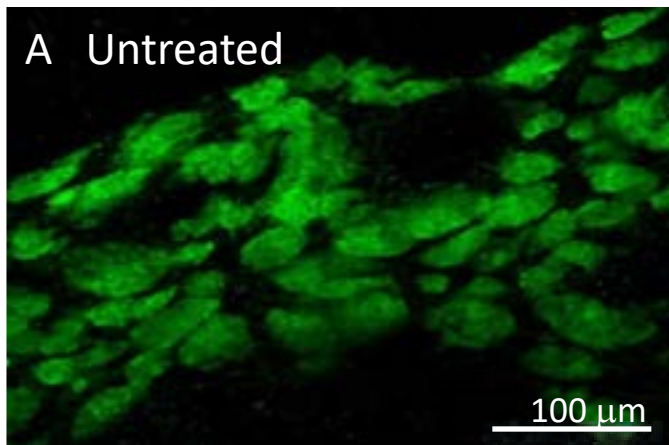
Stojanovska et al, unpublished

Activation of damage-associated molecular patterns: translocation of high mobility group box 1 (HMGB1) protein (mouse)



Stojanovska et al, unpublished

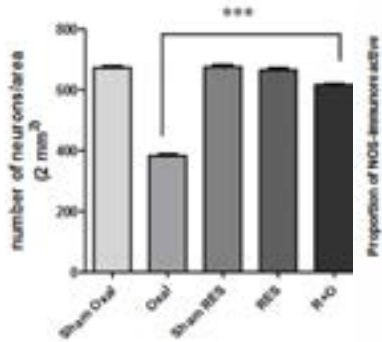
Translocation of Hu protein (human)



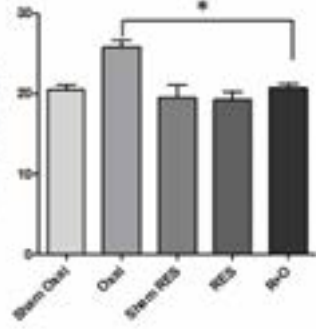
Resveratrol co-treatment alleviates enteric neuropathy, improves colon functions and potentiates anti-cancer efficacy of oxaliplatin

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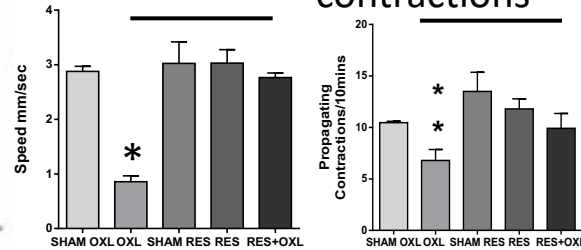
Number of neurons



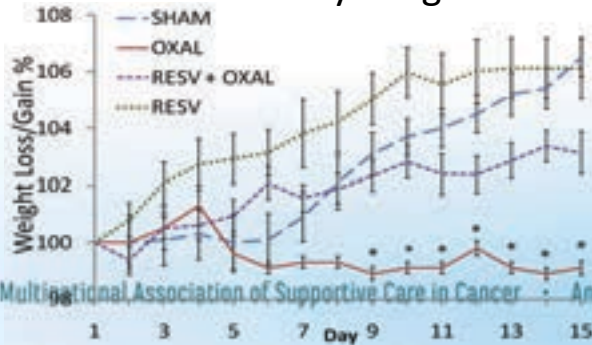
nNOS-IR neurons



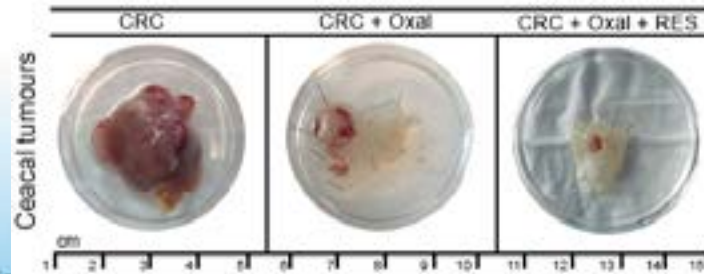
Number and speed of colonic contractions



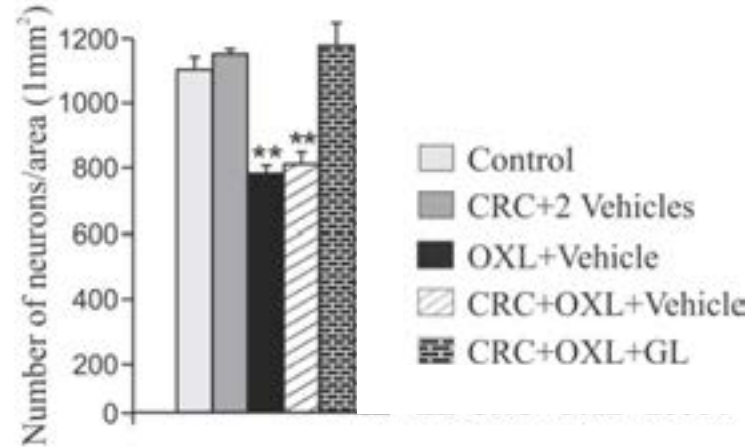
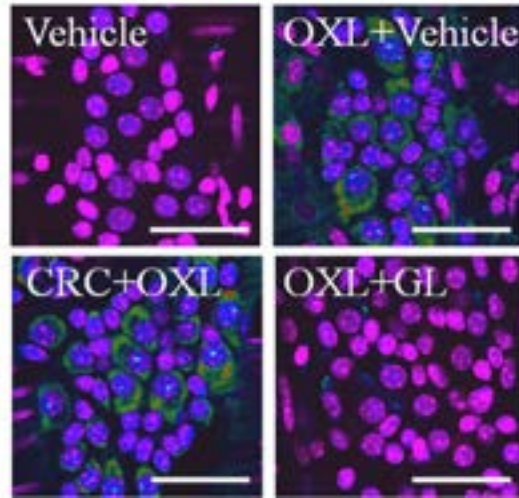
Body weight



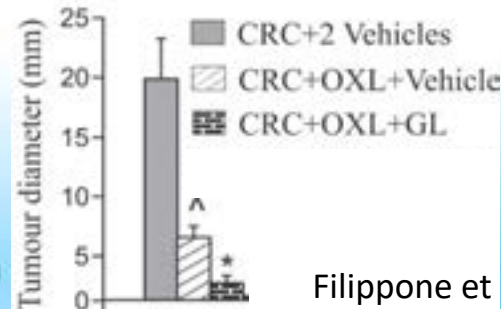
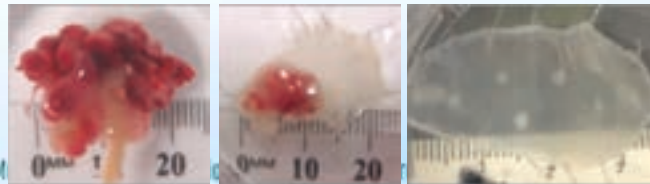
Tumour growth



Co-treatment with HMGB1 inhibitor alleviates enteric neuropathy and inhibits tumour growth



2 vehicles OXL + vehicle OXL + GL



Filippone et al, unpublished



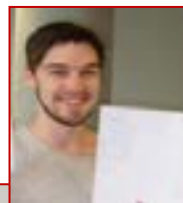
Summary

Chemotherapy induces:

- damage and death of enteric neurons
- changes in neuromuscular transmission and neuronal hyperexcitability
- colonic dysmotility, changes in intestinal transit, symptoms constipation and nausea (pica)
- Oxidative stress and platinum accumulation are major mechanisms of oxaliplatin-induced enteric neuropathy
- Neuroprotective treatments can alleviate gastrointestinal side-effects without compromising anti-cancer efficacy of chemotherapy

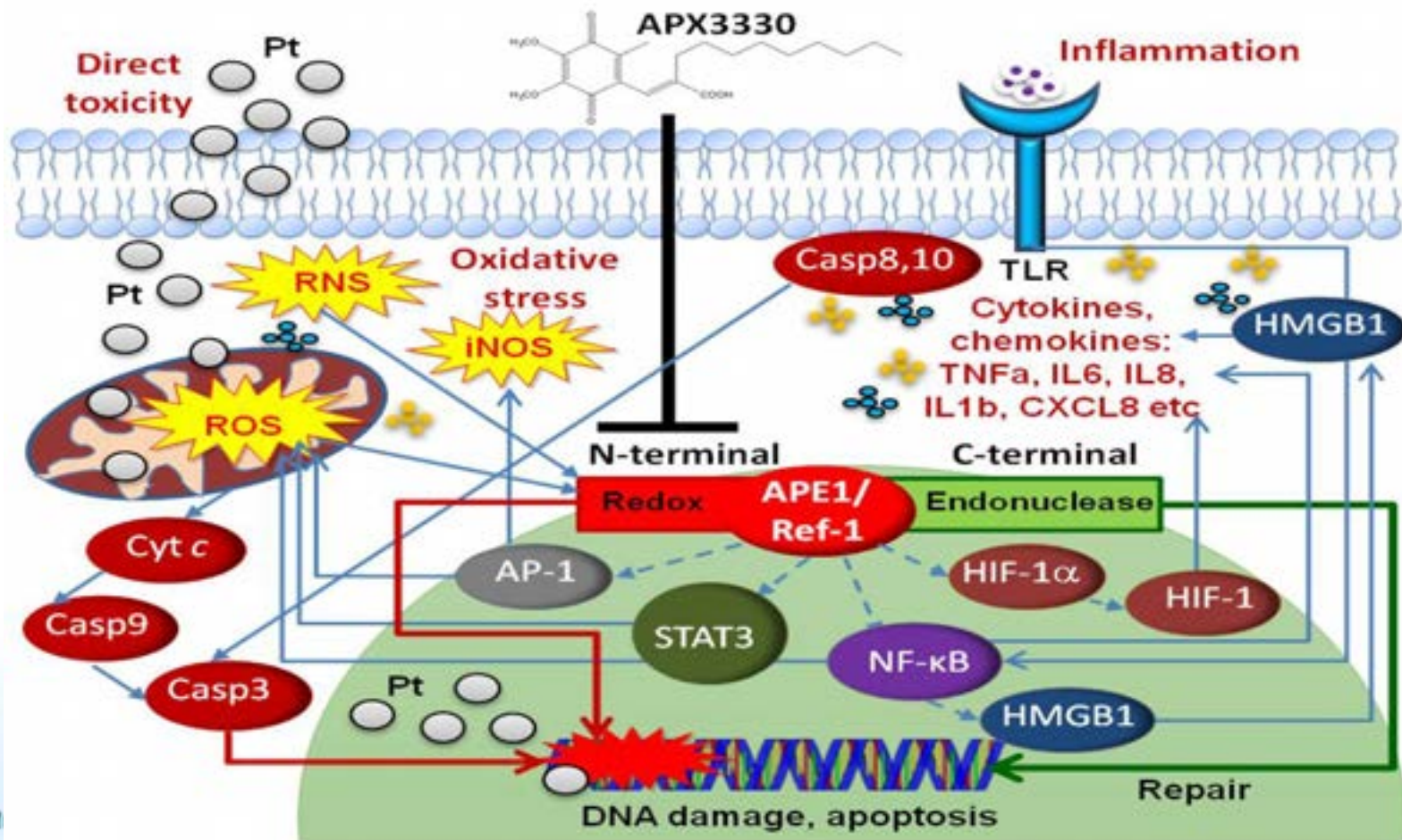


Acknowledgements



- College of Health & Biomedicine
- Centre for Health, Research & Education
- NHMRC
- Victoria University Research Grants



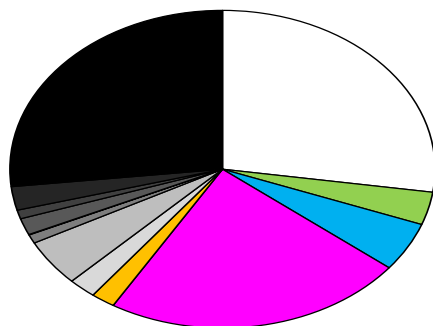
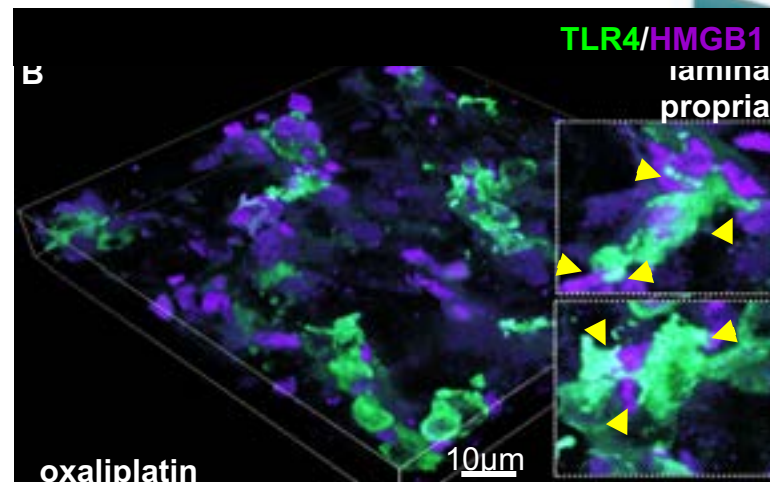
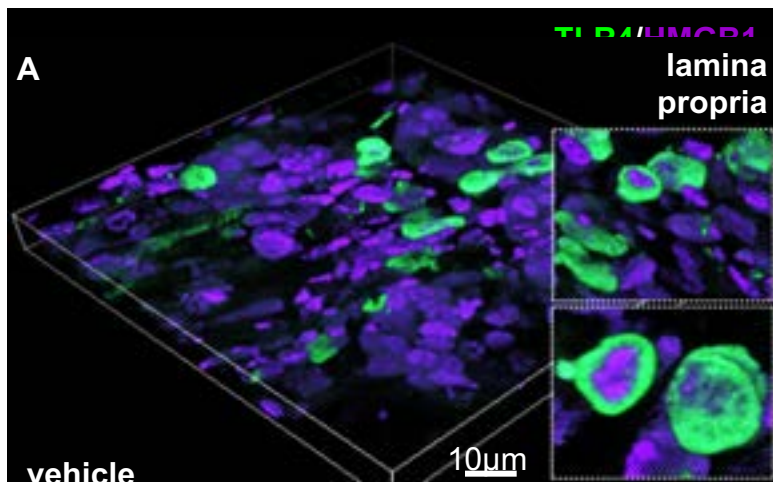


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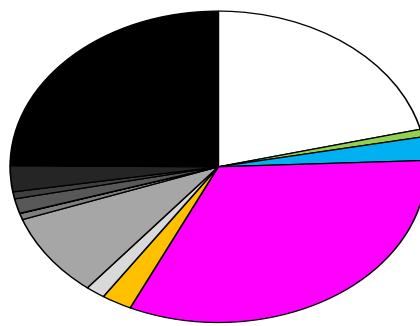
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Changes in Toll-like receptors and gut microbiota



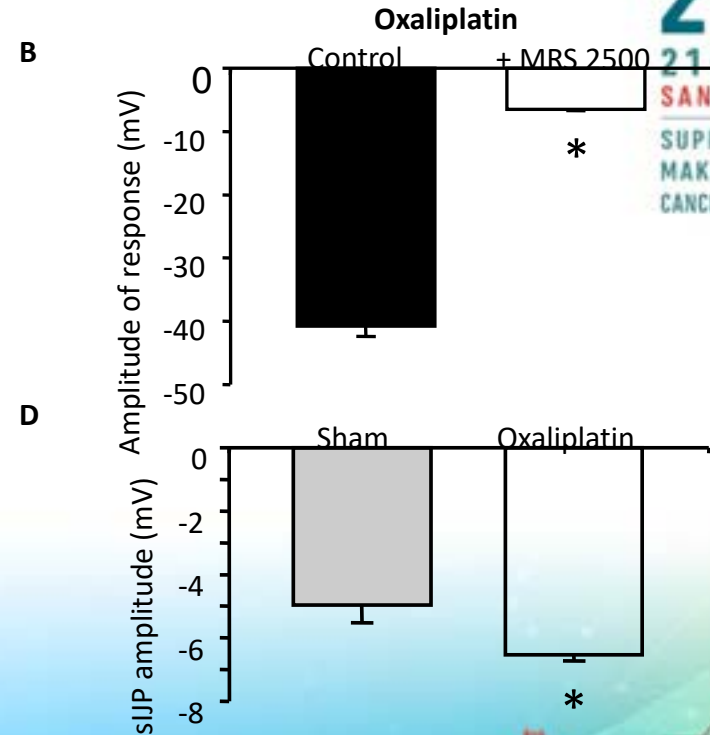
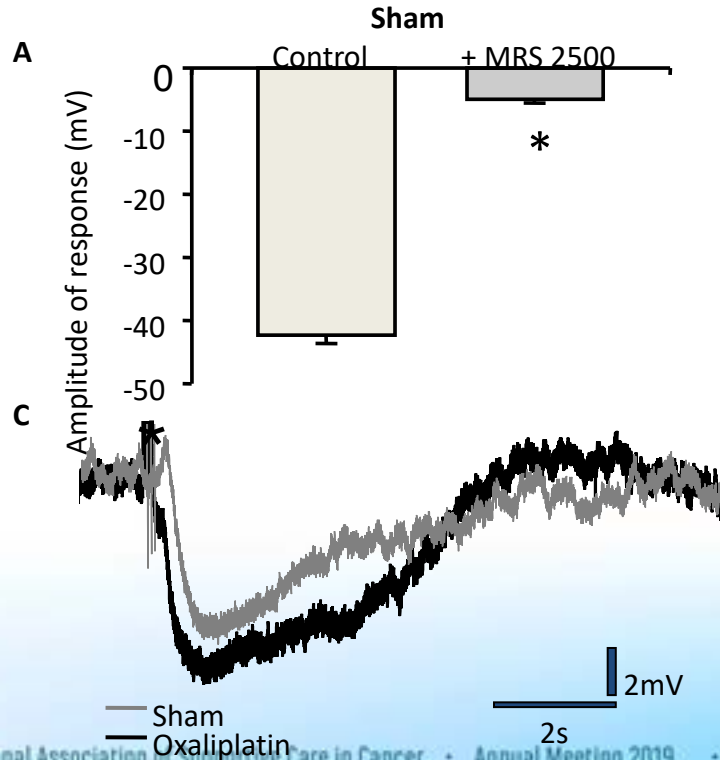
vehicle



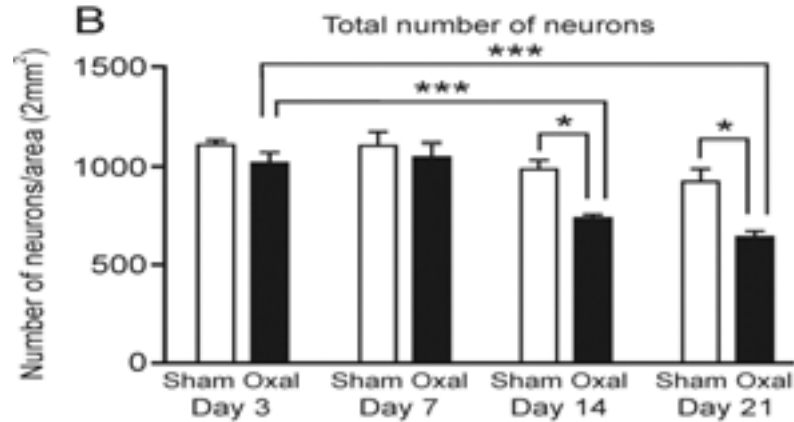
oxaliplatin

- Bacteroides
- **** □ Parabacteroides
- * □ Prevotella1
- * □ Prevotella2
- * □ Odoribacter
- Mucispirillum
- Lactobacillus
- Dehalobacterium
- Ruminococcus
- Sutterella
- Bilophila
- Desulfovibrio
- Other

Effect of oxaliplatin on nitrgergic neuromuscular transmission

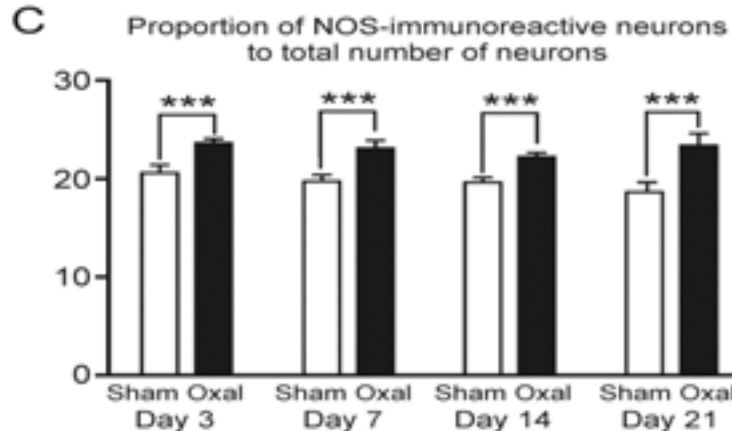
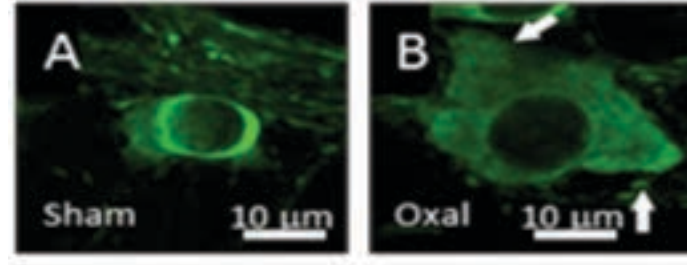


Chemotherapy-induced loss of enteric neurons and changes in nNOS neurons

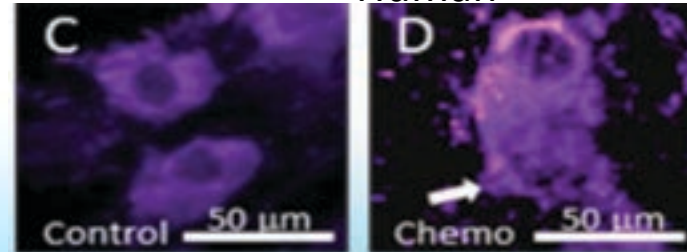


nNOS-IR neurons: morphological changes

Mouse

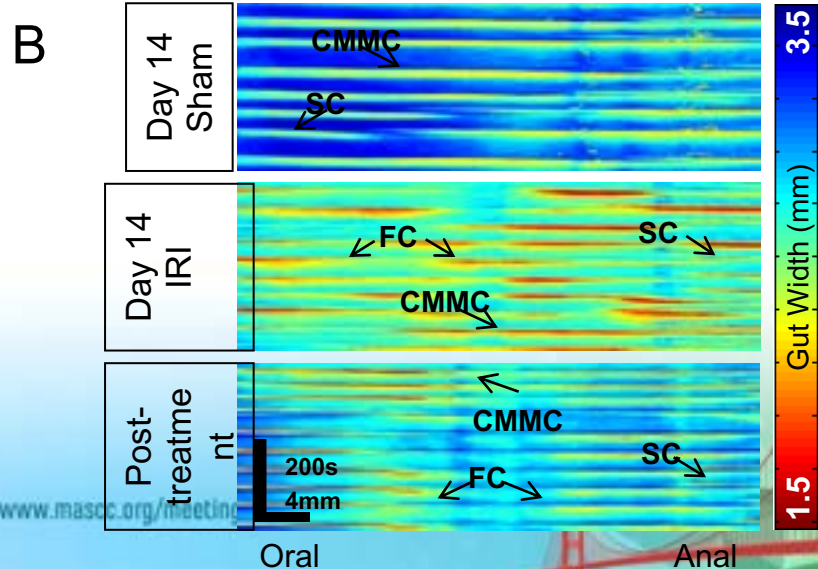
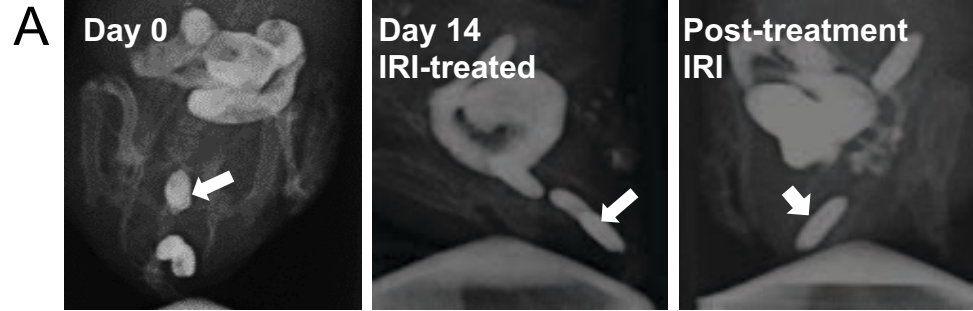
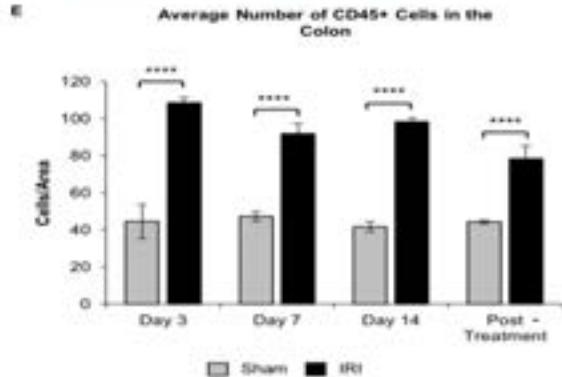
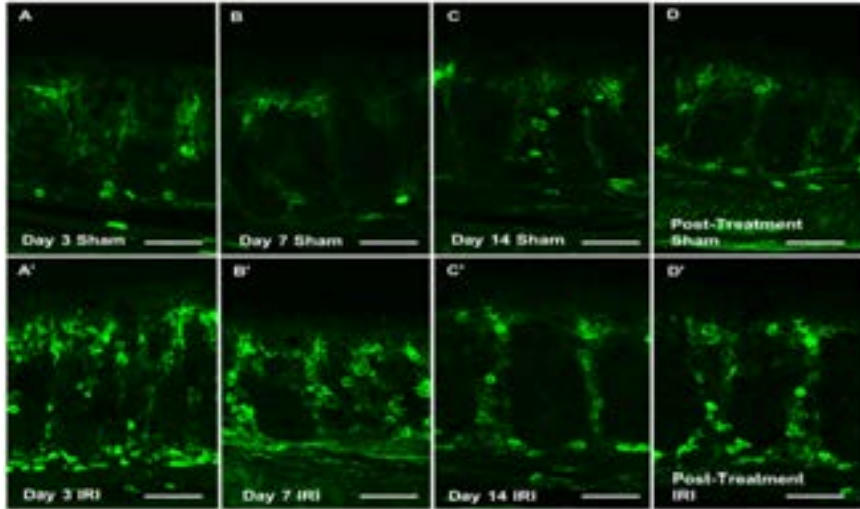


Human

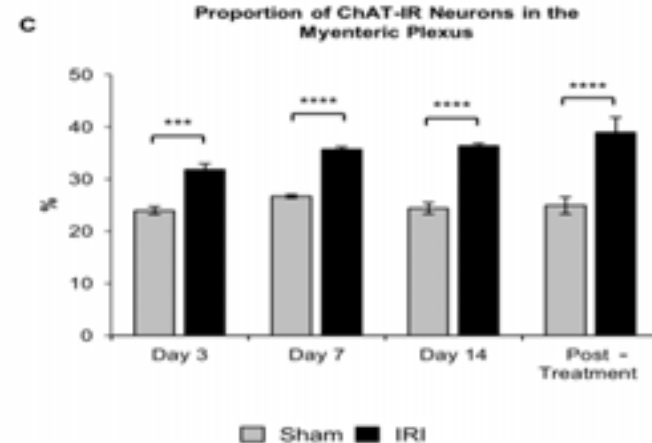
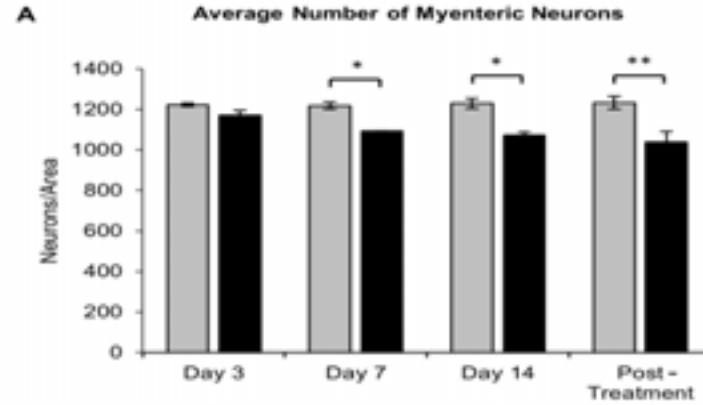
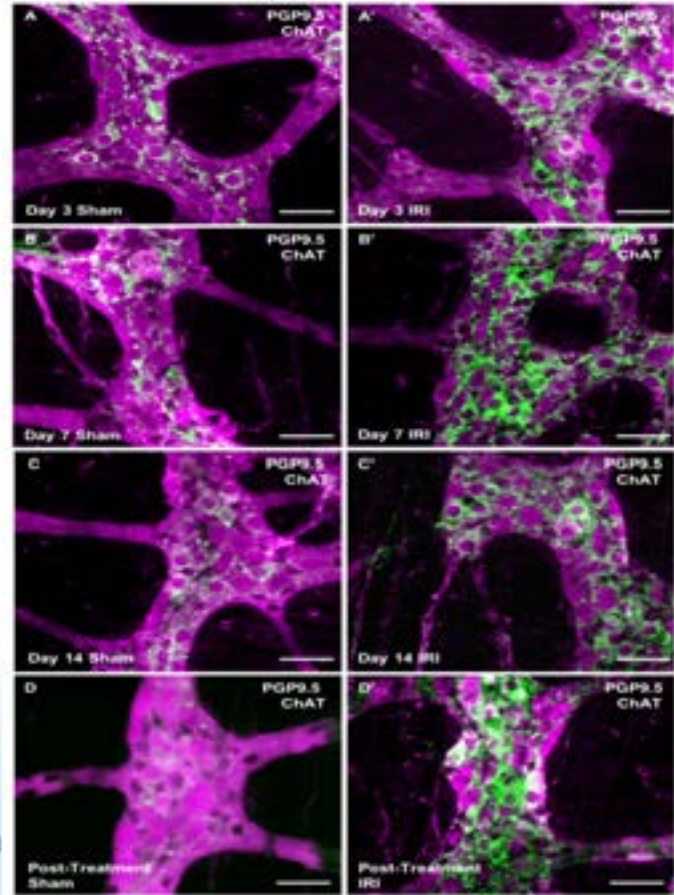


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Irinotecan-induced diarrhoea and mucositis



Irinotecan-induced changes in ChAT neurons

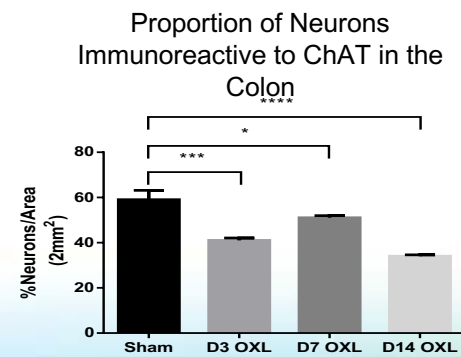
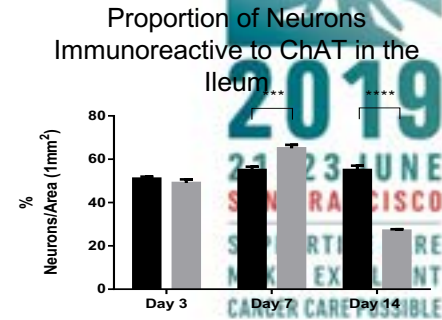
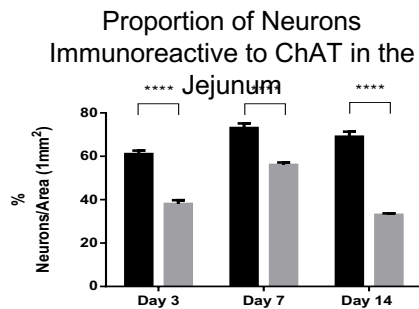
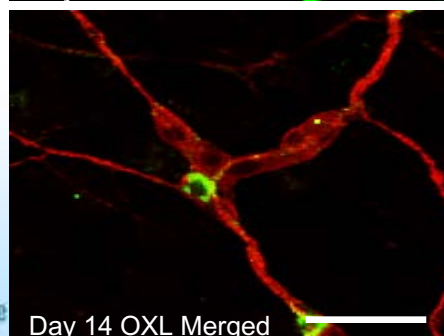
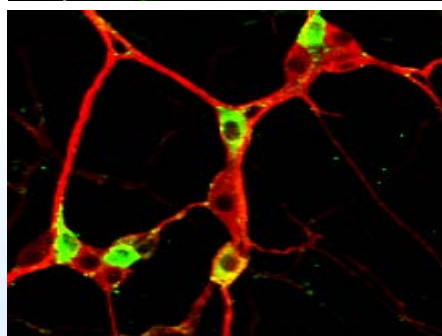
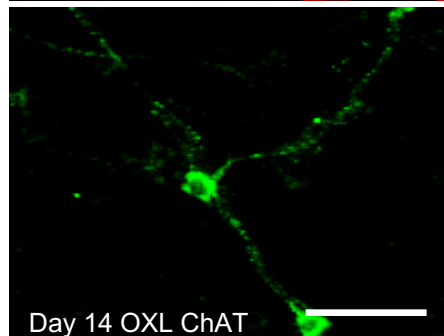
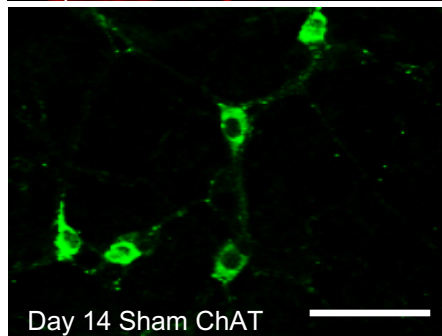
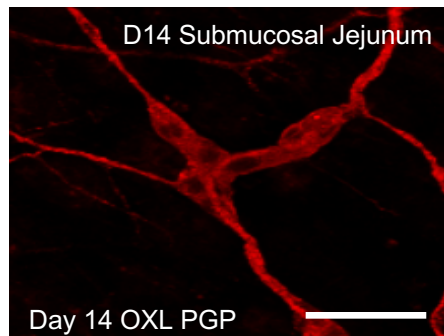
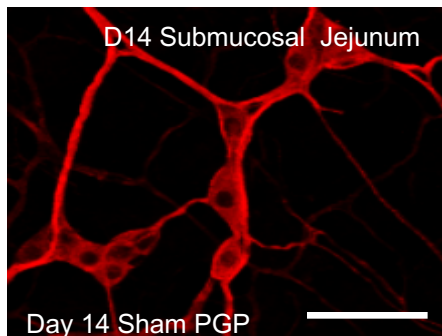


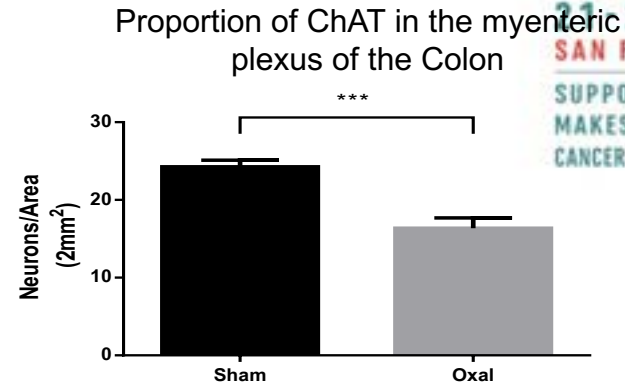
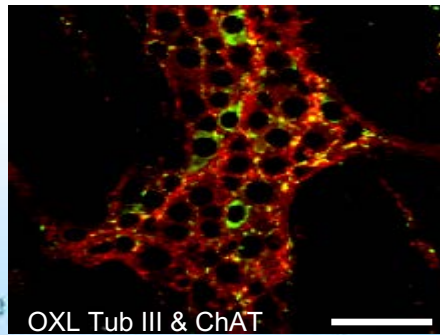
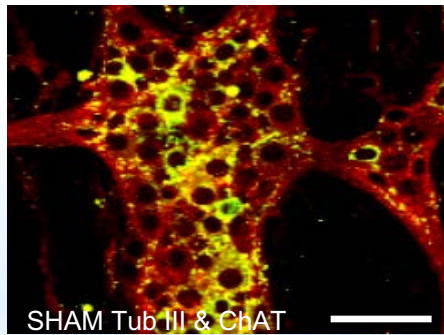
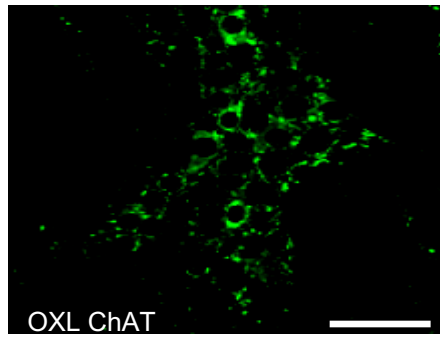
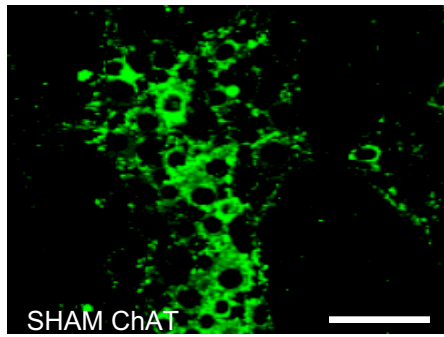
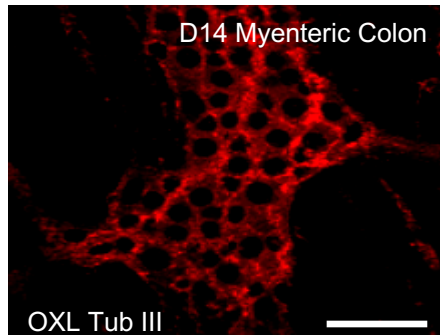
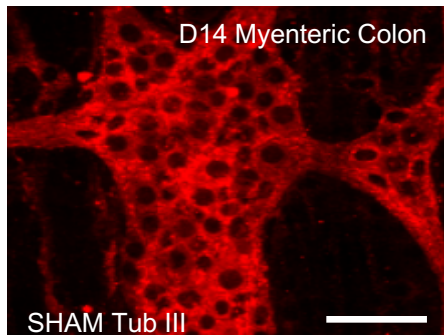
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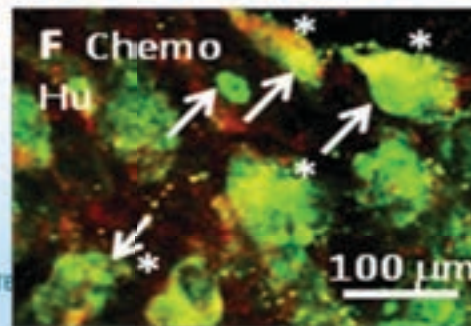
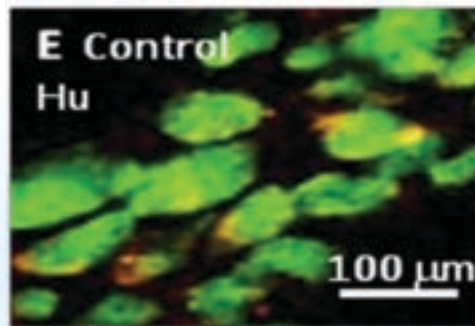
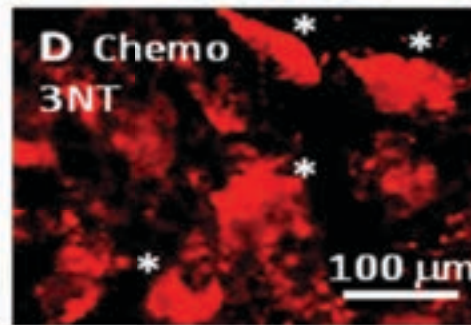
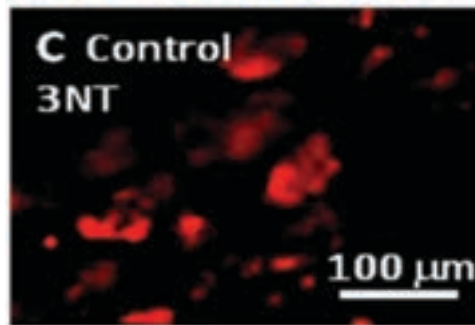
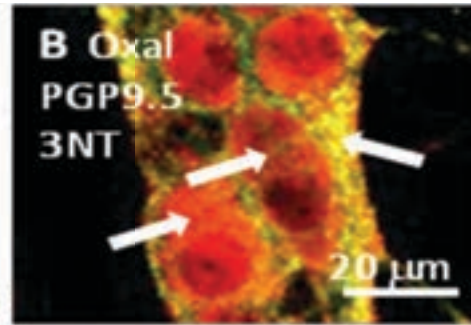
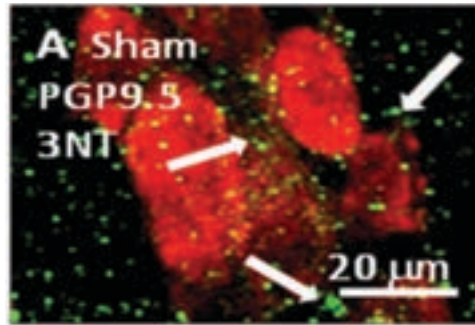
23 JUNE
FRANCISCO

ORTIVE CARE
S EXCELLENT
R CARE POSSIBLE

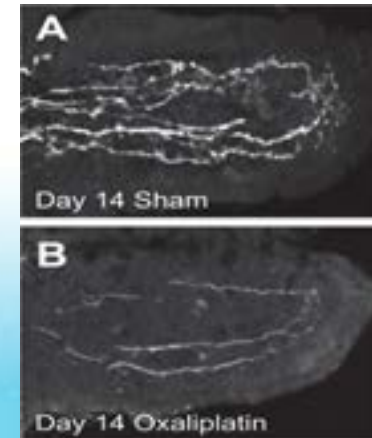






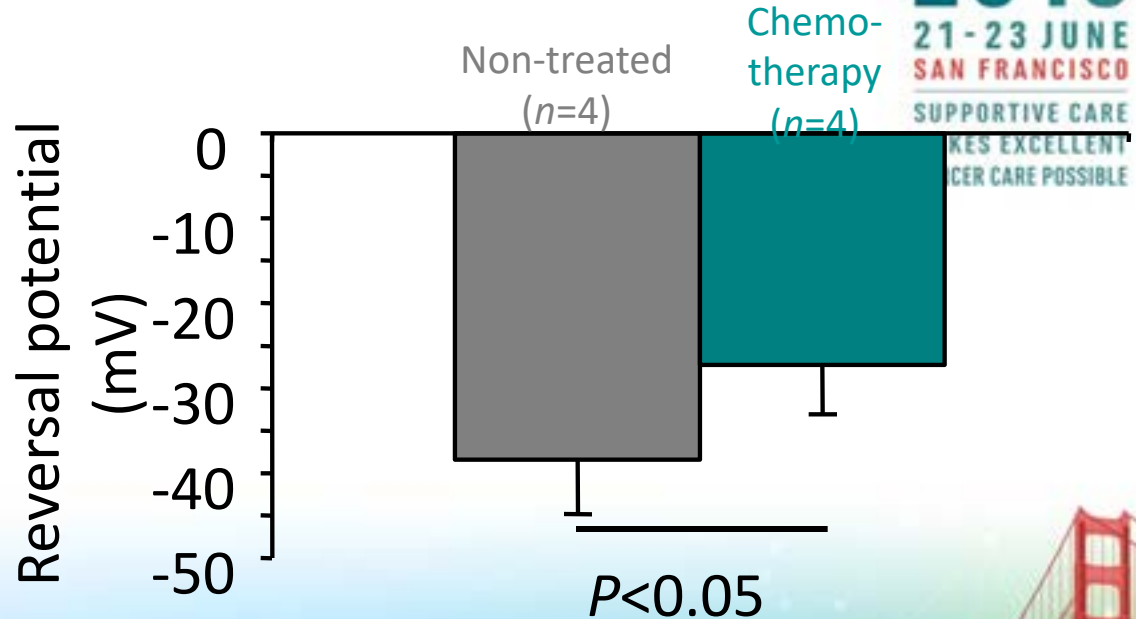
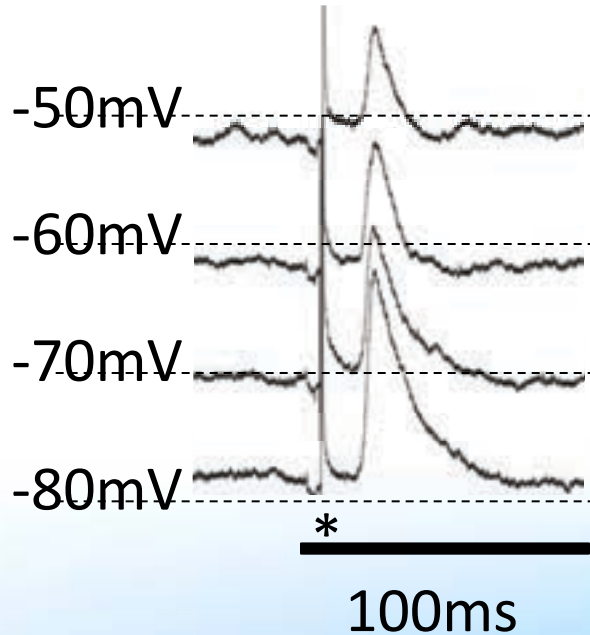


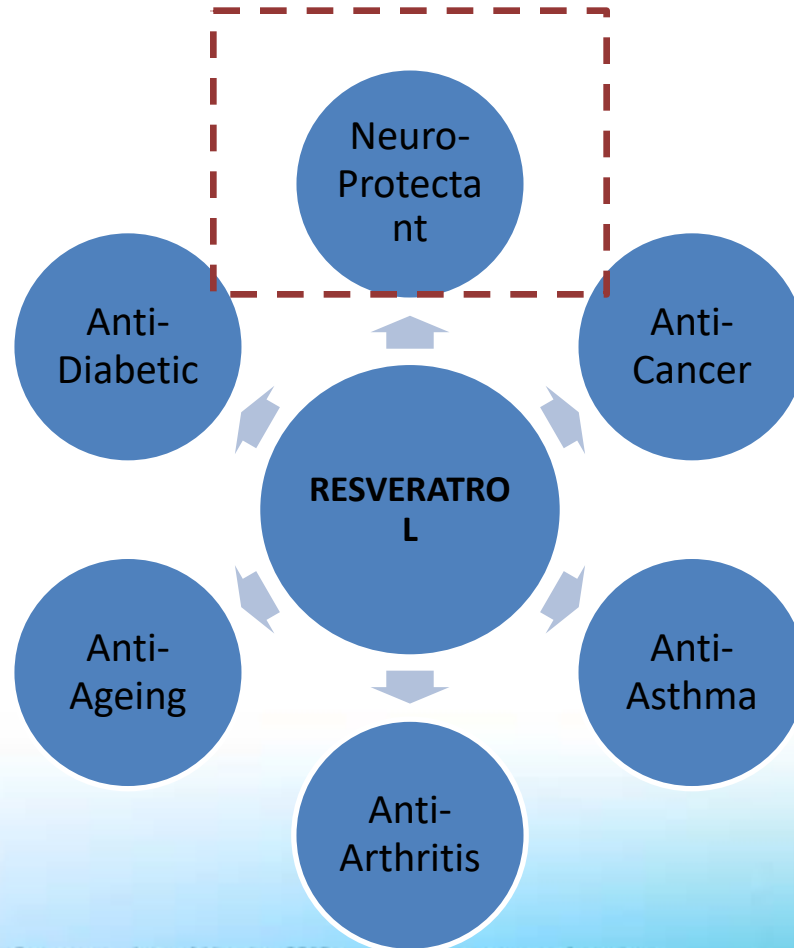
- Aggregates of nitrosylated proteins (mouse, human)
- Translocation of Hu protein from cytoplasm to the nuclei (mouse, human)
- Reduction in fibre density projecting to mucosa (mouse)



2019
21-23 JUNE
SAN FRANCISCO
SUPPORTIVE CARE
EXCELLENT
CANCER CARE POSSIBLE

Fast EPSPs in myenteric S neurons

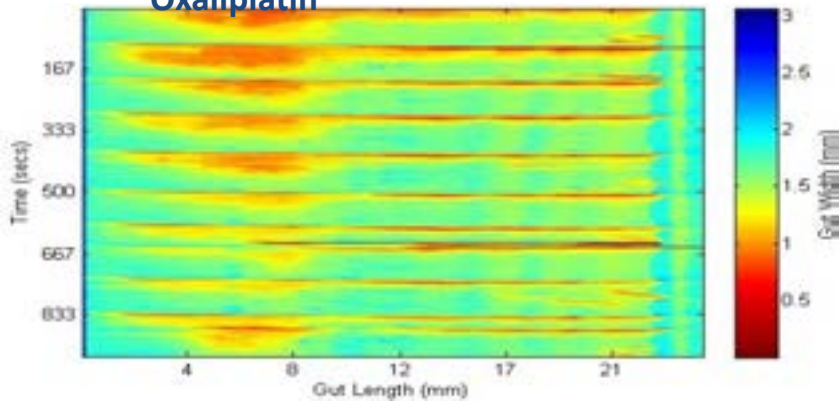




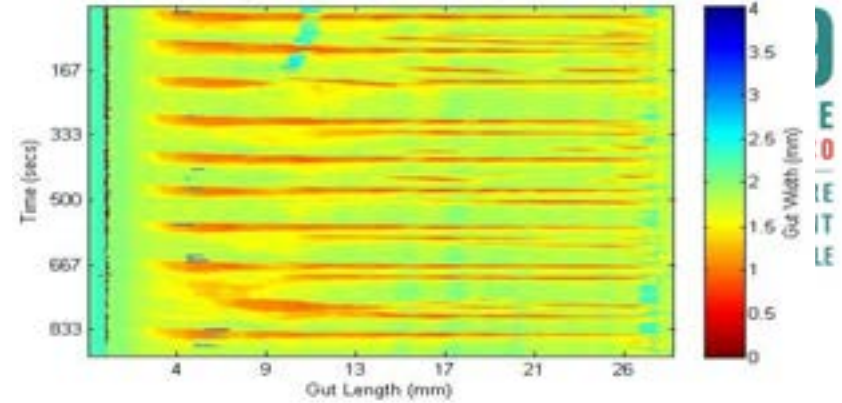
Results: Motility



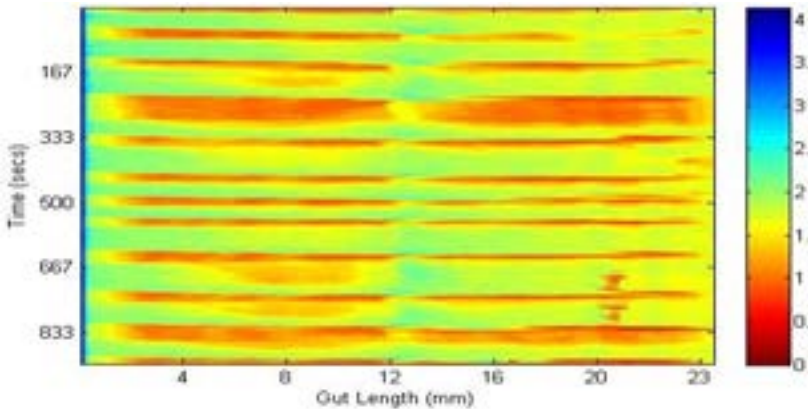
Sham for
Oxaliplatin



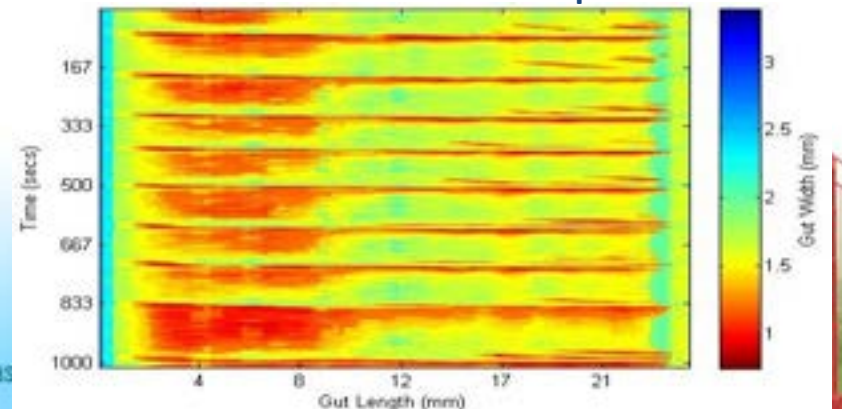
Oxaliplatin



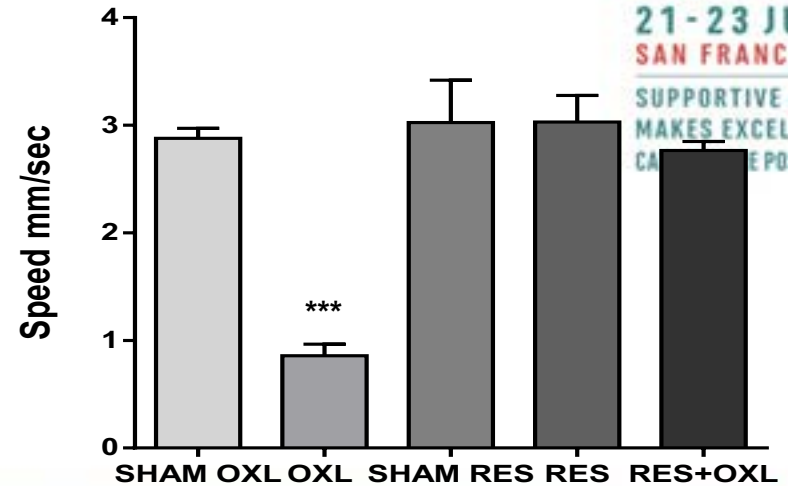
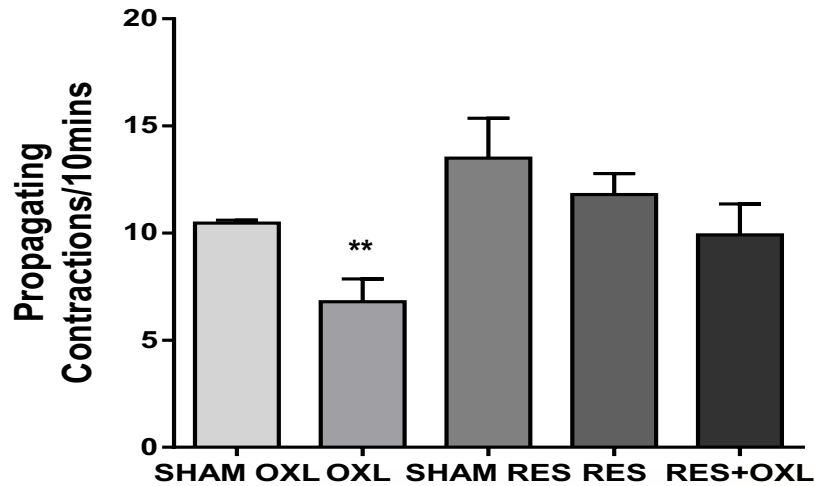
RES



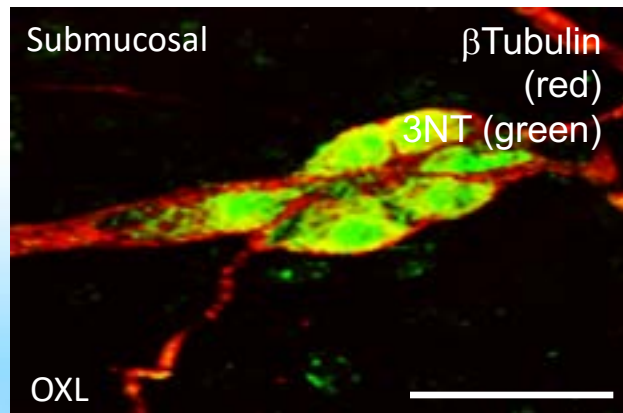
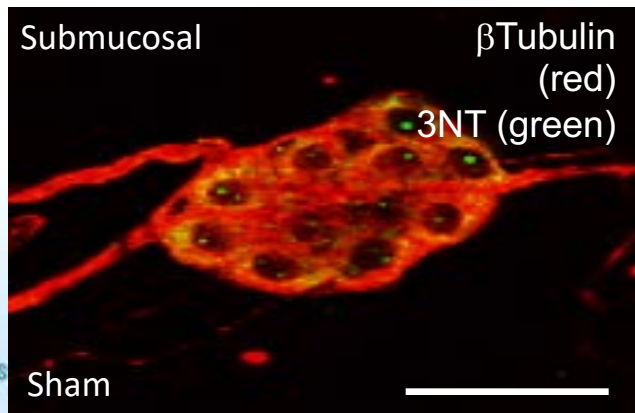
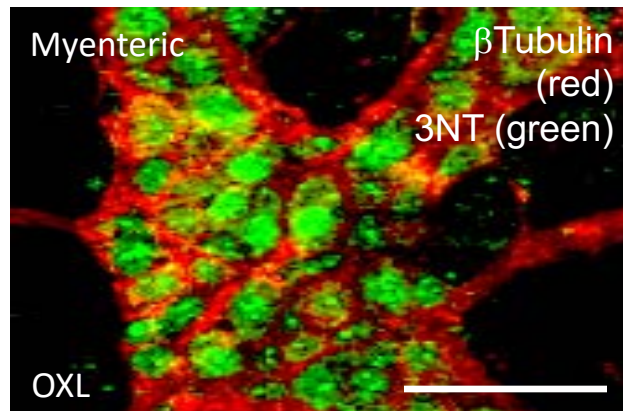
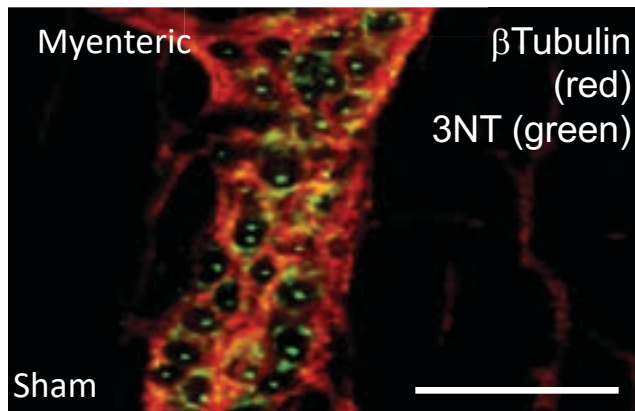
RES + Oxaliplatin



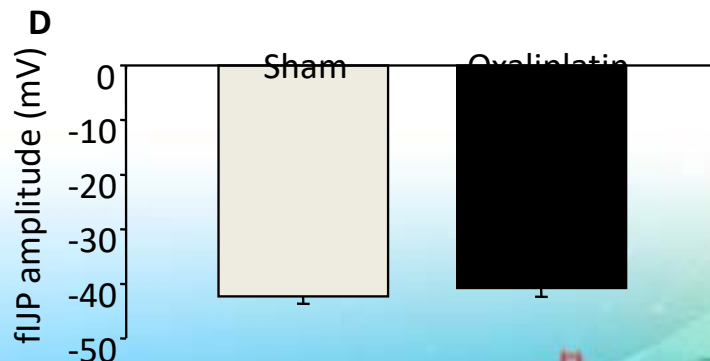
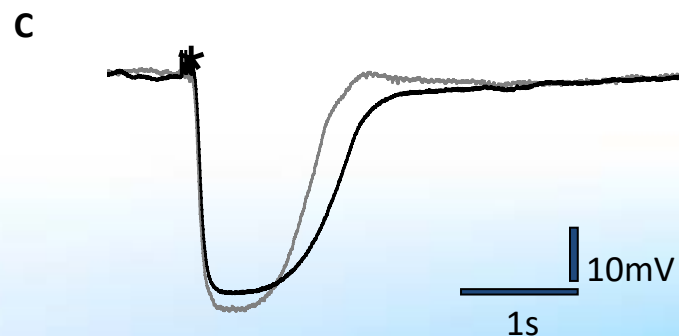
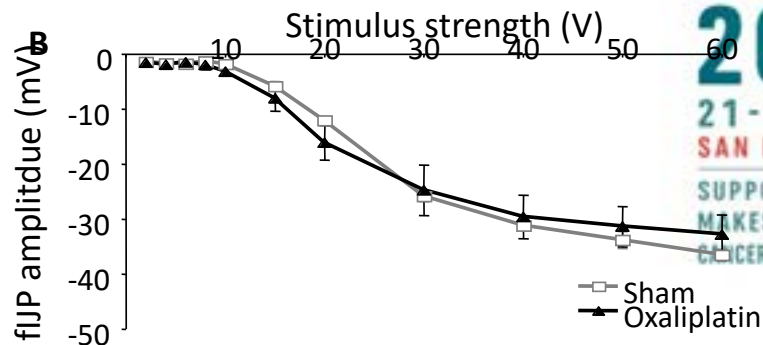
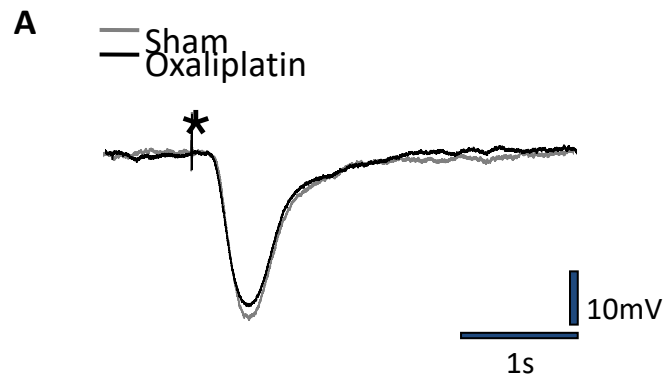
Resveratrol Restored Colon Motility



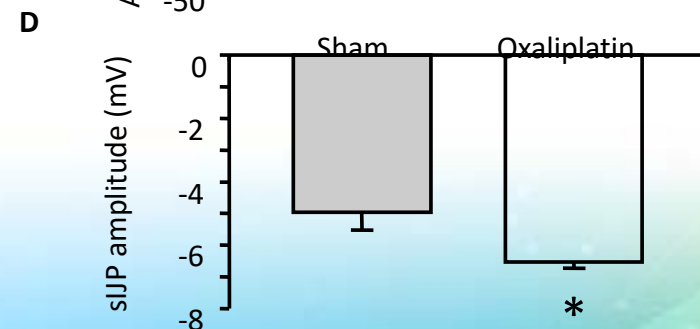
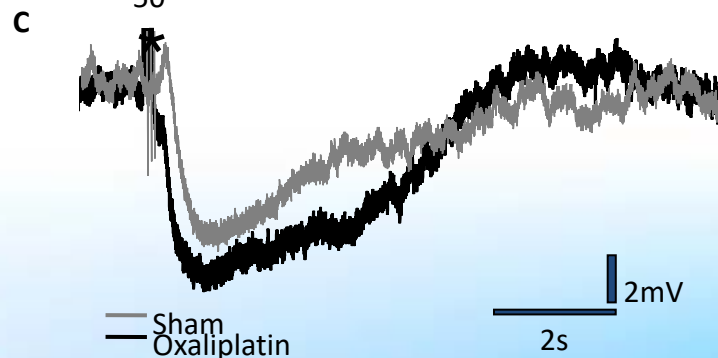
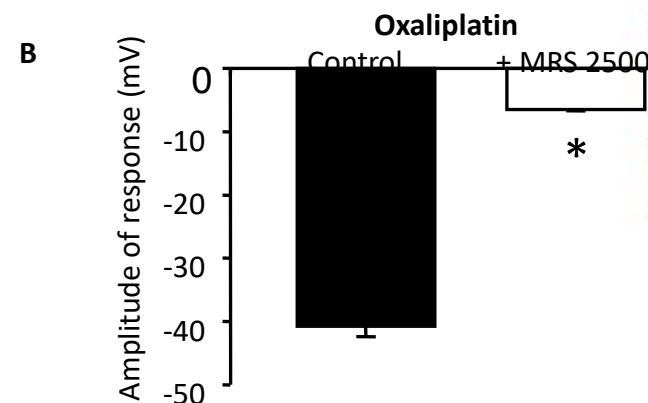
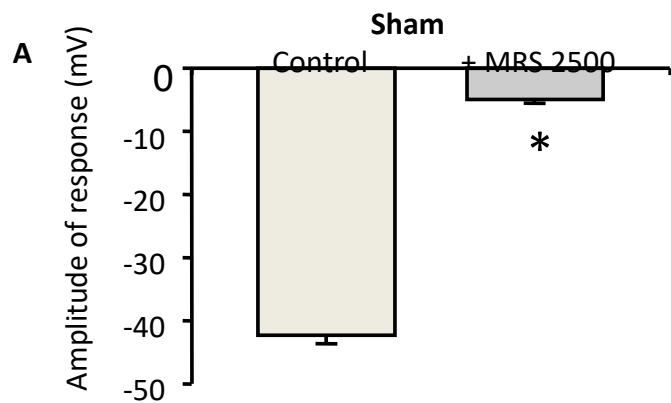
Protein nitrosylation



Effect of oxaliplatin on Purinergic neuromuscular transmission

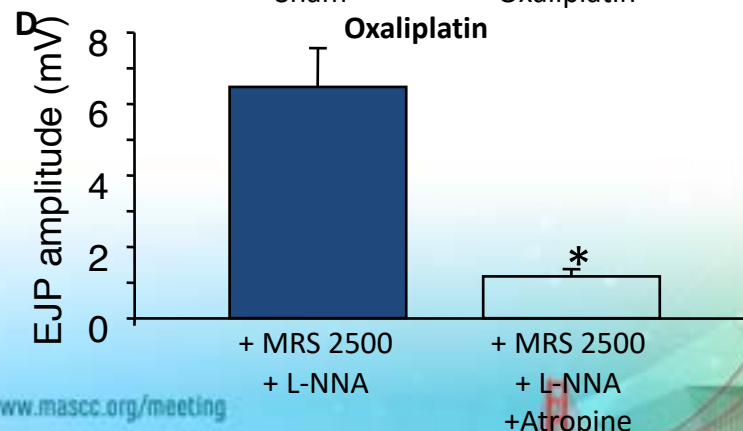
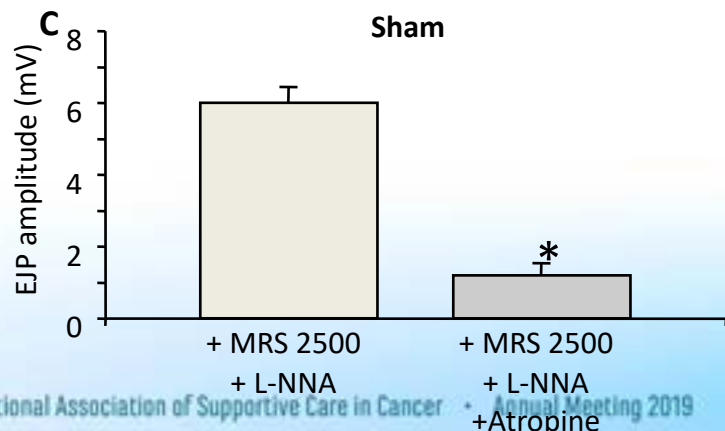
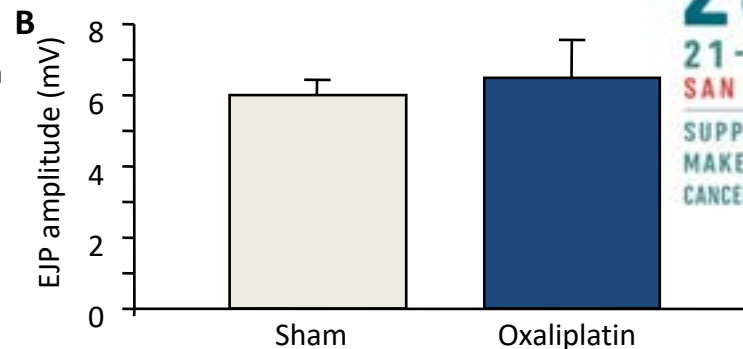
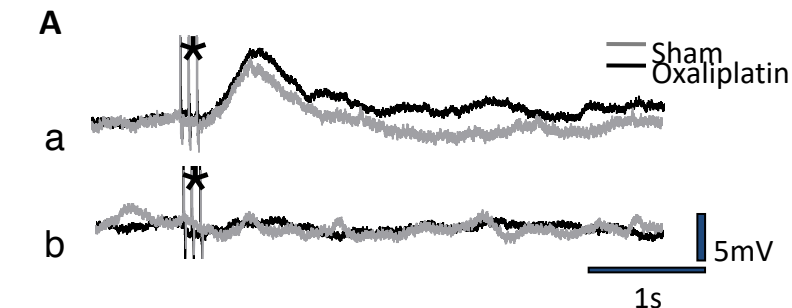


Effect of oxaliplatin on Nitroergic Neuromuscular Transmission

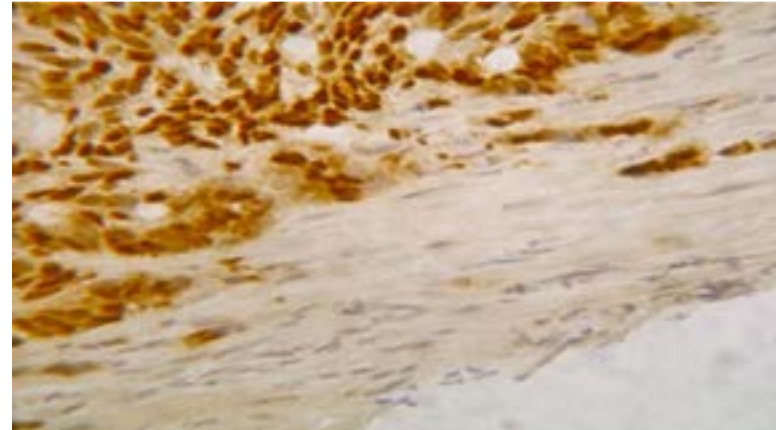
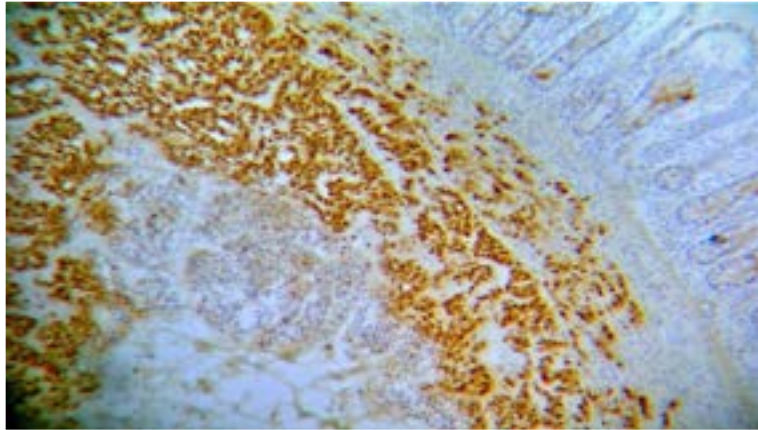


Oxaliplatin increased the amplitude of slow Inhibitory Junction Potentials (sIJP)

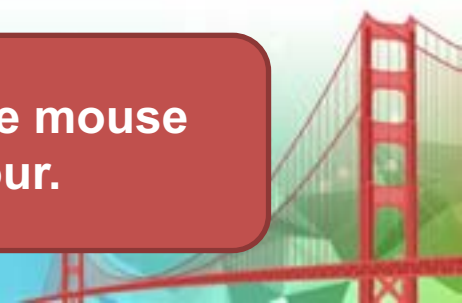
Effect of oxaliplatin on Cholinergic Neuromuscular Transmission



Growth of Tumour in the Caecum & Colon

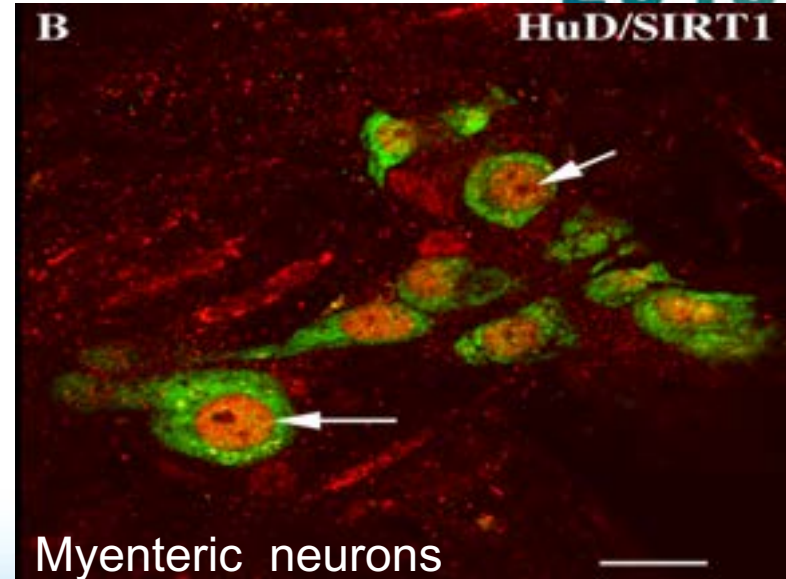


HT29 human cancer cell lines stain darker against the mouse tissue, confirming the presence of cancer/tumour.



Resveratrol

- **Natural polyphenolic compound** (grape skin and red wine)
- **Strong antioxidant properties**
- **A sirtuin-activating compound** (an enzyme that deacetylates proteins that contribute to cellular regulation)
- **Stimulates responses to molecular damage and metabolic imbalances**
- **Prevents apoptosis in brain neurons**
- **Neuroprotective activity** (Alzheimer's, Parkinson's)
- **Has minimal or no toxicity** on the body systems



Lakhan SE, Kirchgessner A
Journal of Translational Medicine 2011, 9:202