New Strategies for Managing Neurotoxic Treatment Related Complications

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Consulting Disclosures

- Asahi Kasei Pharma Corp
- Metys Pharma
- PledPharma

Clinical Cancer Research

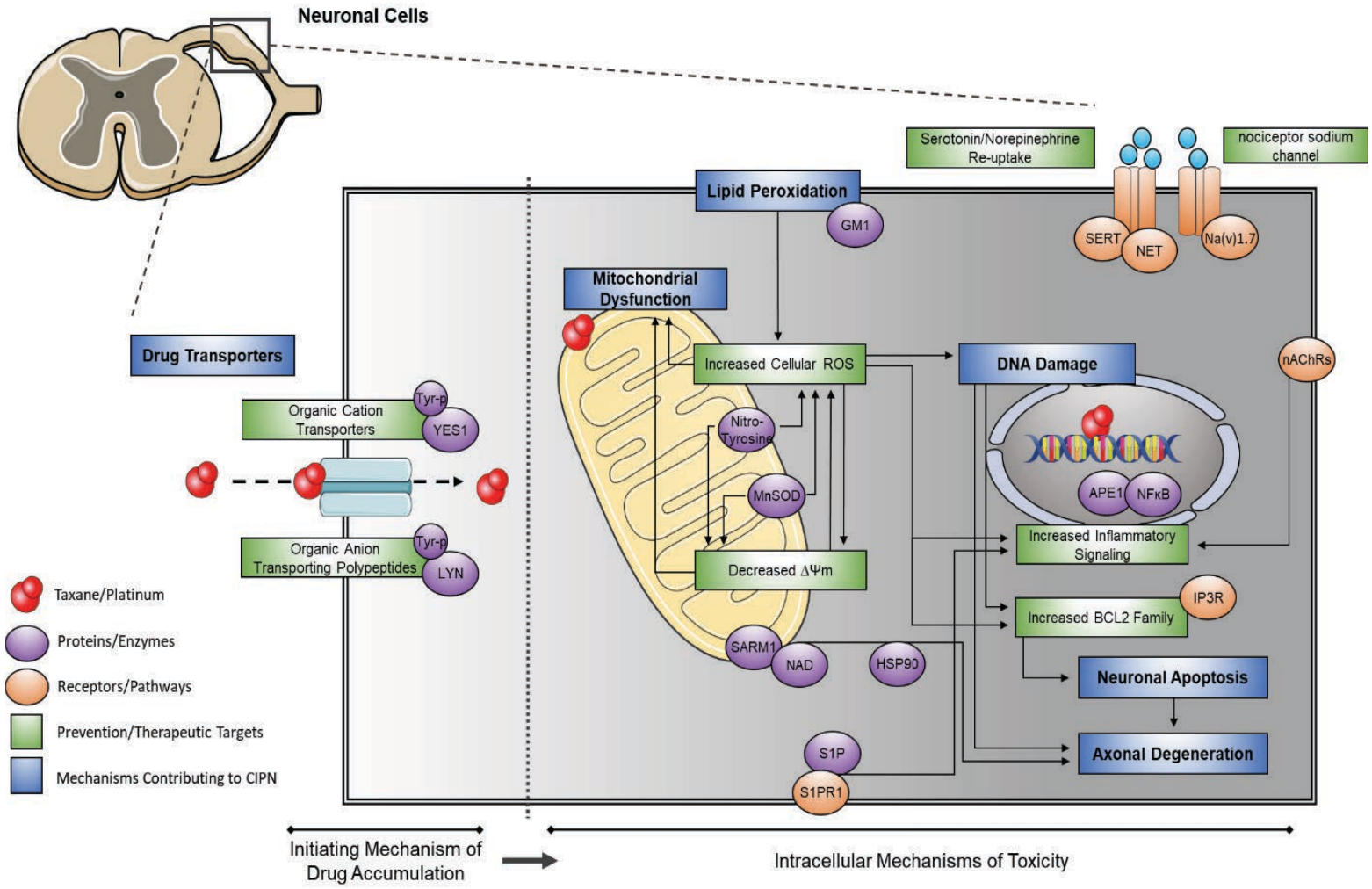
Reviews

Recent developments of novel pharmacologic therapeutics for prevention of chemotherapy-induced peripheral neuropathy

Shuiying Hu, Kevin M Huang, Elizabeth J Adams, Charles L Loprinzi, and Maryam B Lustberg

Topics

- **Introduction**
- Targeting neuronal uptake transporters
- Mitochondrial enzyme and oxidative stress
- Targeting apurinic/apyrimidinic endonuclease (APE1) function
- Inhibition of neuro-inflammatory processes in the spinal cord
- Targeting the ganglioside-monosialic acid (GM-1) pathway
- Serotonin-norepinephrine reuptake and nociceptor sodium channel inhibition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Axonal Degeneration
Taxane/Platinum
Proteins/Enzymes
Receptors/Pathways
Prevention/Therapeutic Targets
Mechanisms Contributing to CIPN
Initiating Mechanism of Drug Accumulation
Intracellular Mechanisms of Toxicity

Emerging Clinical Trials for the Prevention of CIPN

- Nilotinib
- Dasatinib
- Calmangafodipir
- APX3330
- Fingolimod
- Duloxetine
- GM-1

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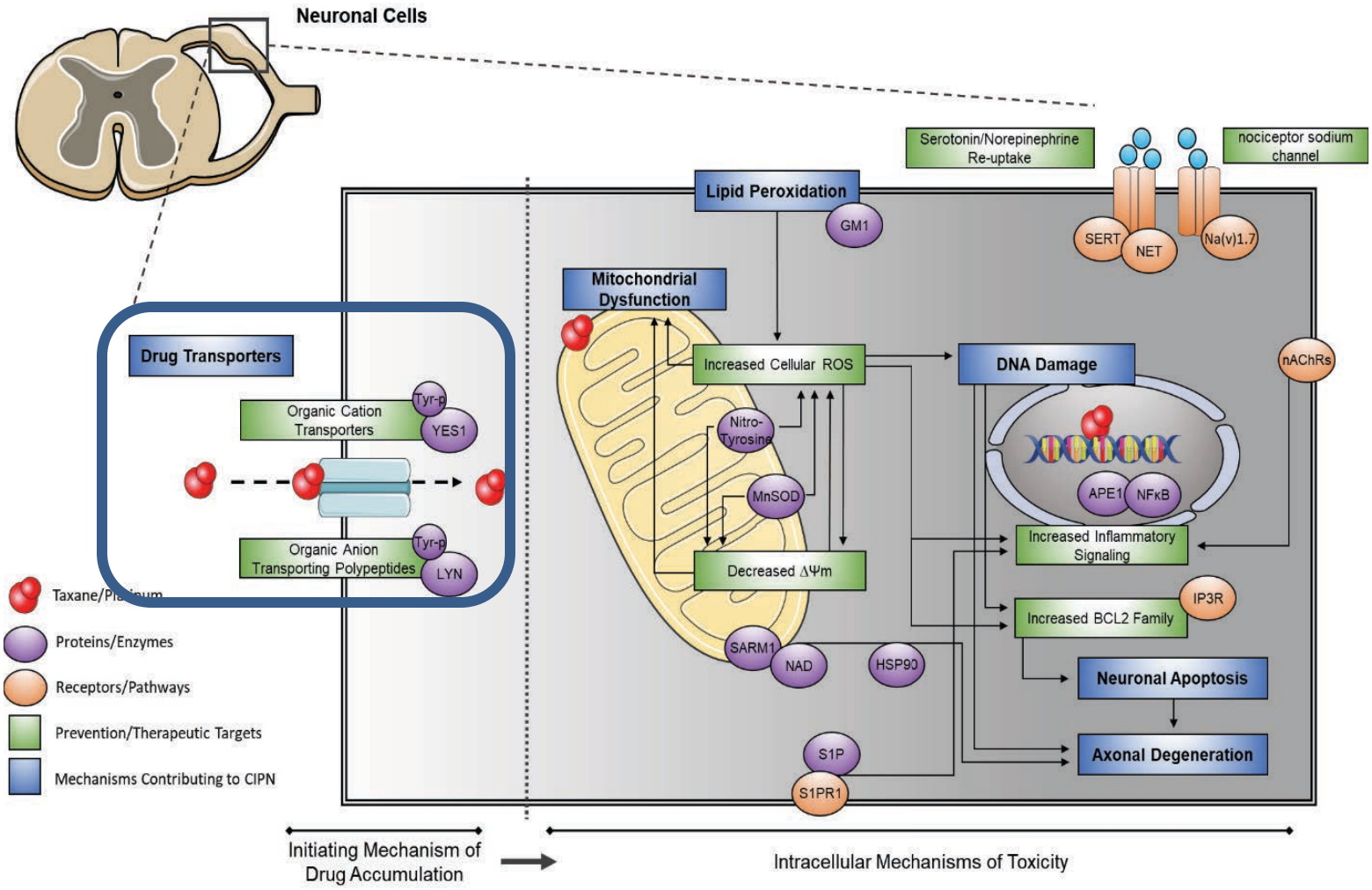
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- Facilitated transport mechanisms are responsible for chemotherapeutic drugs to get into DRGs

- Transmembrane transport of chemotherapy
  - Taxanes by specific organic anion transporting polypeptides (OATPs)
  - Platinum drugs by organic cation transporters (OCTs)

- Preclinical studies show that transporter-mediated uptake of chemo into DRGs triggers sensory neuron damage

- Genetic or pharmacological knockout of transporters localized to the DRG in mice protect against CIPN from paclitaxel, vincristine, and oxaliplatin

- Small-molecule library screens have identified that FDA-approved TKIs block these uptake transporters, in vitro and in vivo

- Proof-of-principle studies with nilotinib (an OATP1B2 inhibitor) and dasatinib (an OCT2 inhibitor) support
  - CIPN inhibition
  - Without affecting chemo drug clearance
  - No negative effect on antitumor efficacy

Emerging Clinical Trials for the Prevention of CIPN

Intervention	Target/Pathway	N	Patient Population
Nilotinib	OATP1B1-3 uptake transporter inhibitor	95	Breast cancer patients initiating paclitaxel
Dasatinib	OCT2 uptake transporter inhibitor	20	Stage 4 colorectal patients initiating oxaliplatin-based therapy

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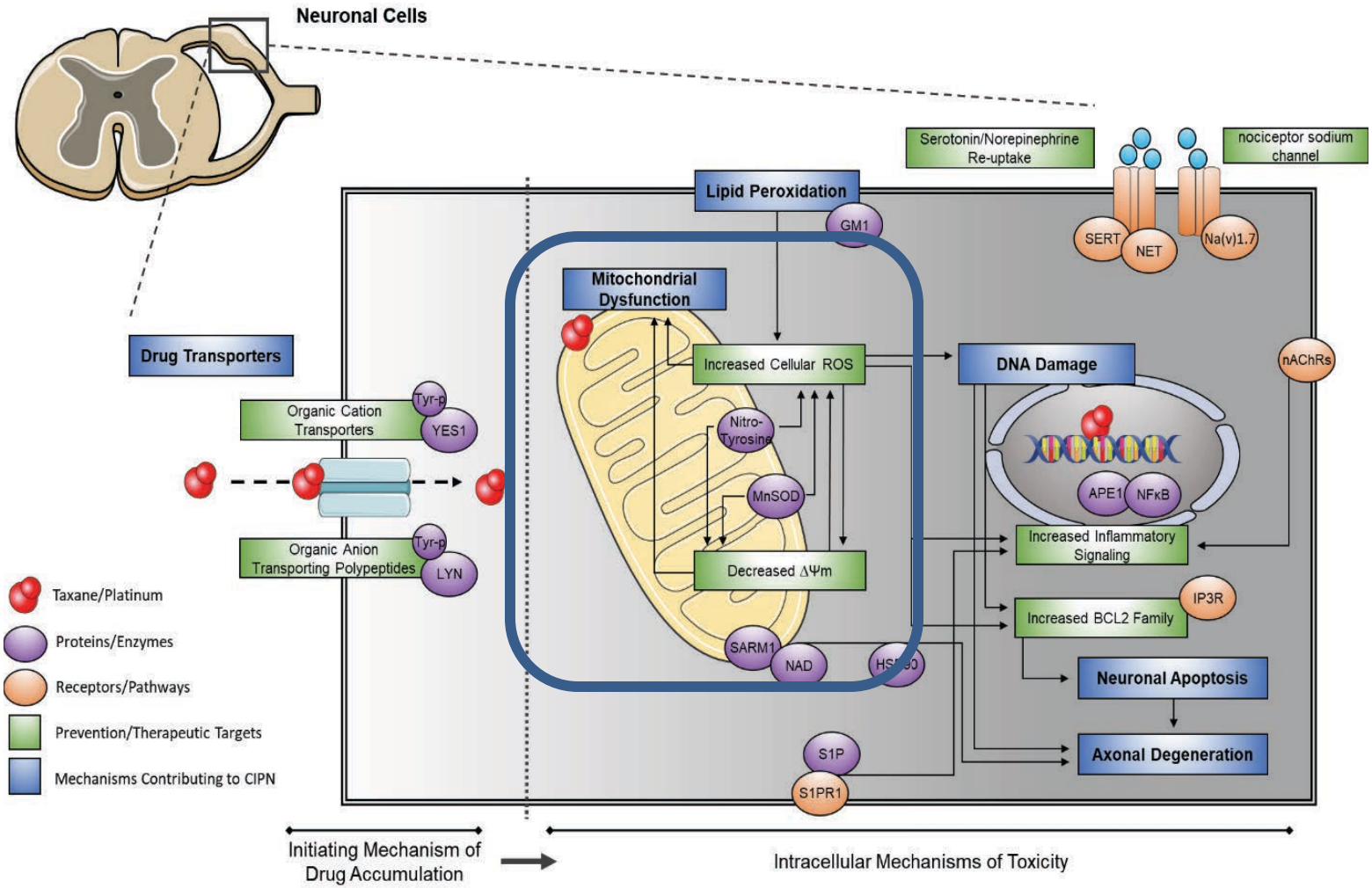
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- Neuronal mitochondrial injury promotes somatosensory neuron degeneration via oxidative stress

- Calmangafodipir
  - Derived from mangafodipir, an MRI contrast agent
  - Reduces reactive oxygen species and subsequent nerve injury
  - Preclinical data strongest with platinum agents
  - In a PC, DB R phase II study in patients with metastatic colorectal cancer
    - Calmangafodipir reduced cold allodynia and other sensory symptoms
    - PFI and OS looked good

Emerging Clinical Trials for the Prevention and Treatment of CIPN

Intervention	Target/Pathway	N	Patient Population
Calmangafodipir	Reduction of ROS	420	Stage 4 colorectal patients initiating oxaliplatin-based therapy (POLAR M)
		280	Adjuvant oxaliplatin based therapy (POLAR A)

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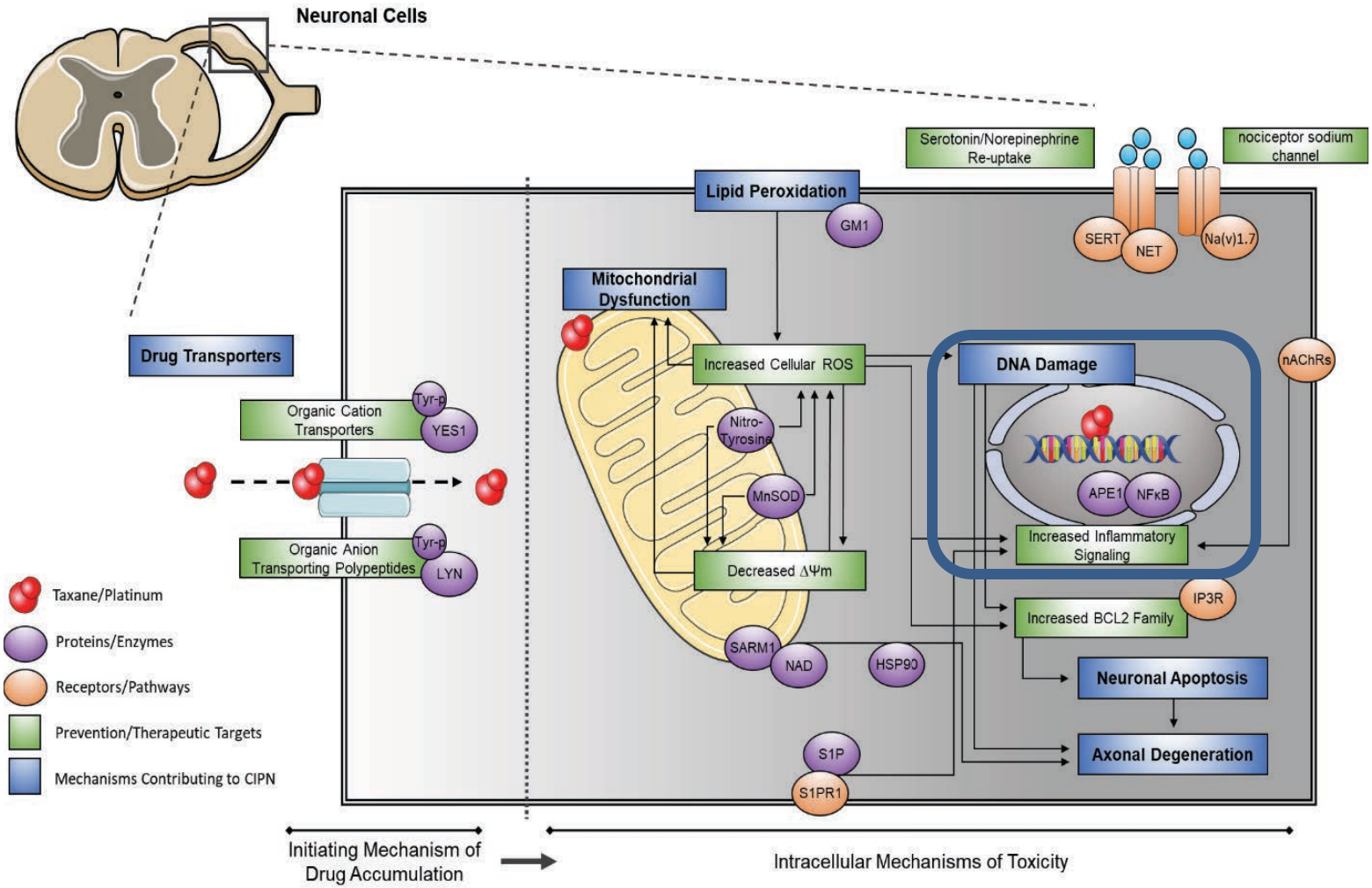
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- Drug-induced DNA damage in sensory neurons causes CIPN, particularly from cisplatin and oxaliplatin
- This produces significant ROS and oxidative DNA damage
- The base excision repair pathway is the primary means for repairing oxidative DNA damage
- An enzyme called APE1 (apyrimidinic endonuclease/redox effector factor) is important for the removal of damaged DNA bases and blocking inflammation inducing transcription factors

- Decreased expression of the APE1 repair enzyme in sensory neurons increases neurotoxicity

- A first-in-class small molecule APE1 modifier, APX3330, is neuroprotective

- APX3330 also appears to have anti-cancer activity

Emerging Clinical Trials for the Prevention of CIPN

Intervention	Target/Pathway	N	Patient Population
APX3330	Enhances APE1 DNA oxidative DNA repair activity and blocks inflammatory TF activation	30	Adjuvant oxaliplatin-based therapy

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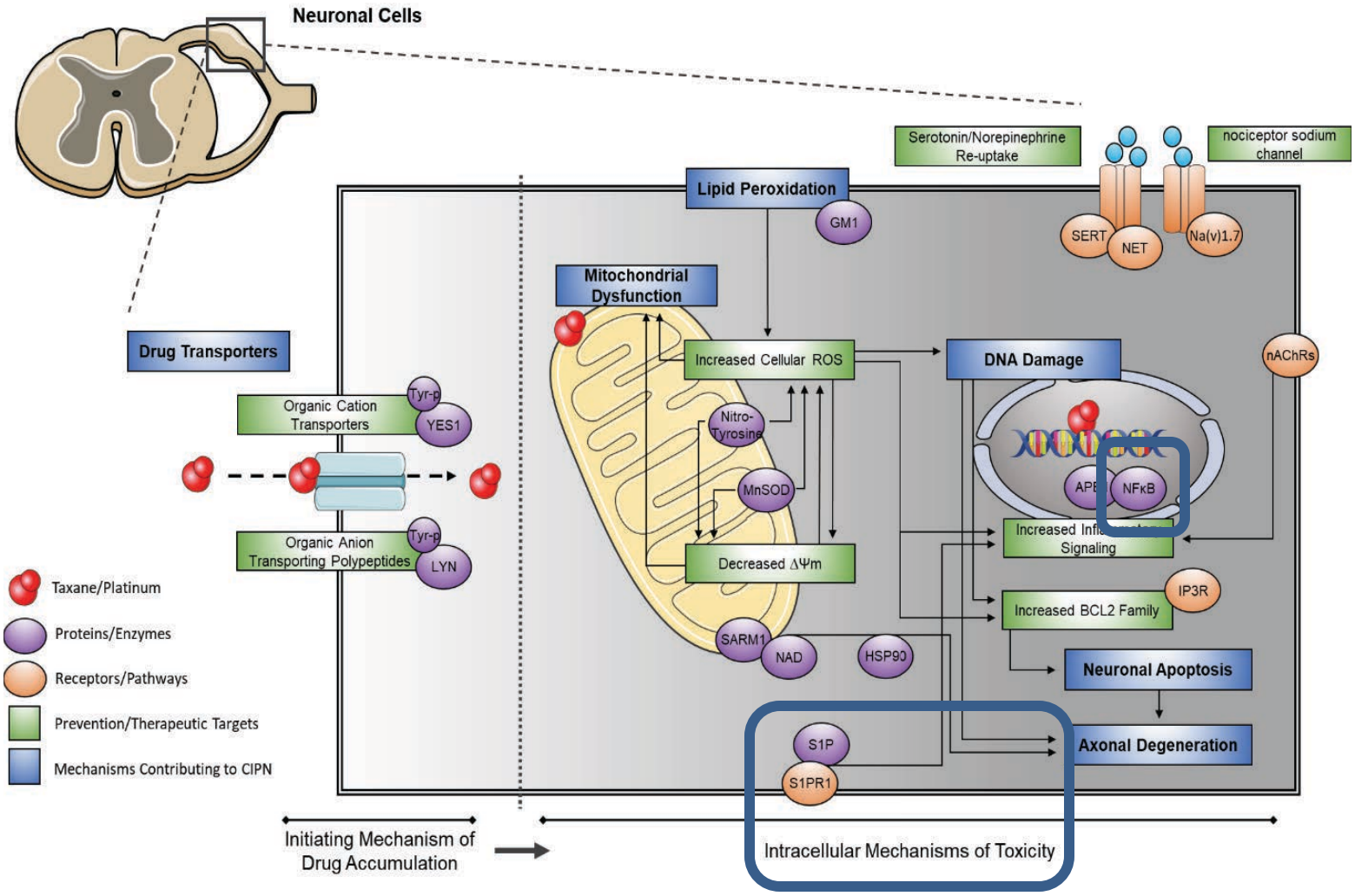
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- Certain neuropathic chemotherapy classes drive the development of CIPN by dysregulating sphingolipid metabolism, leading to increased formation of S1P, which binds and activates S1PR1 (sphingosine-1-phosphate receptor 1)
  - Increases NF*K*B and P38 kinase
  - Increases glial cell activation
  - Increases inflammatory cytokines (TNF and IL-1B)

- Fingolimod, an approved drug for preventing multiple sclerosis-associated neuropathy, is a functional sphingosine-1-phosphate receptor 1 (S1PR1) antagonist

- The downstream effect of S1PR1 blockade is the inhibition of neuro-inflammatory processes in the spinal cord
  - Decreased NF*K*B and P38 kinase
  - Decreased glial cell activation
  - Decreased inflammatory cytokines (TNF and IL-1B)

- In animal models, oral fingolimod can both prevent and treat neuropathic pain from a variety of chemotherapeutic agents

- Fingolimod does not interfere with antitumor efficacy of chemotherapy and may have synergistic antitumor properties

Emerging Clinical Trials for the Prevention and Treatment of CIPN

Intervention	Target/Pathway	N	Patient Population
Fingolimod	S1PR1 antagonism	1) 20	1) Breast cancer patients initiating adjuvant paclitaxel
		2) 10	2) Patients with established long-standing CIPN

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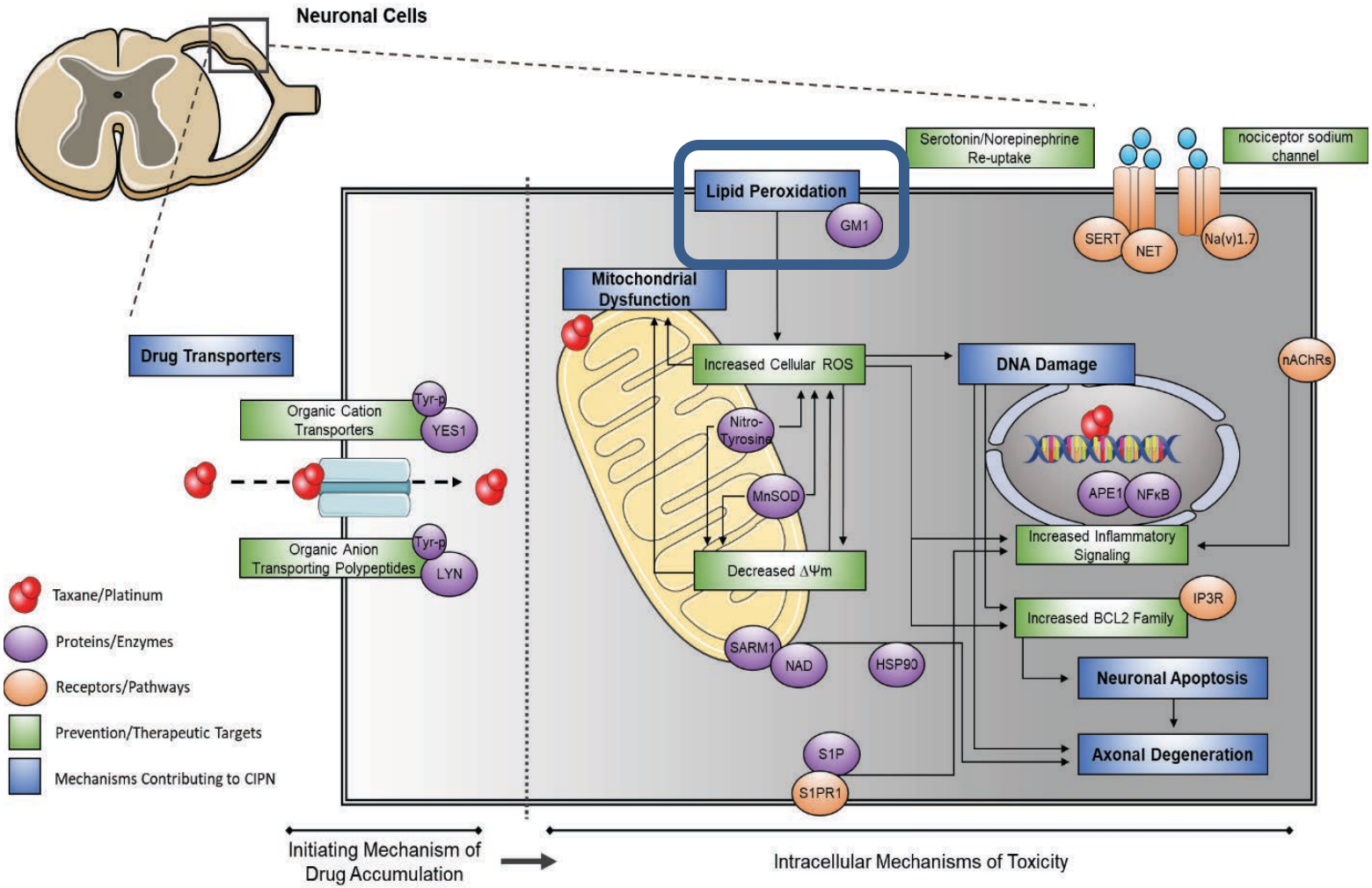
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- Ganglioside-monosialic acid (GM1) is a type of glycosphingolipid, located in the outer layer of the plasma membrane

- GM1 is critical for nerve development, differentiation and repair after injury

- Some data support that it decreases neuro-inflammatory responses

- In preclinical studies, GM1 has been effective for the prevention of CIPN

- A retrospective study supported that GM1 was associated with less oxaliplatin-associated acute and chronic neurotoxicity

Chen XF, Wang R, Yin YM et al; The effect of monosialotetrahexosylganglioside (GM1) in prevention of oxaliplatin induced neurotoxicity: a retrospective study. Biomed Pharmacother 2012; 66:279.

- In the first published randomized clinical trial, 120 patients with GI cancers received oxaliplatin with GM1 or with standard of care (no placebo)
  - GM1 was associated with a modest benefit in preventing high grade neuropathy from oxaliplatin-induced neurotoxicity

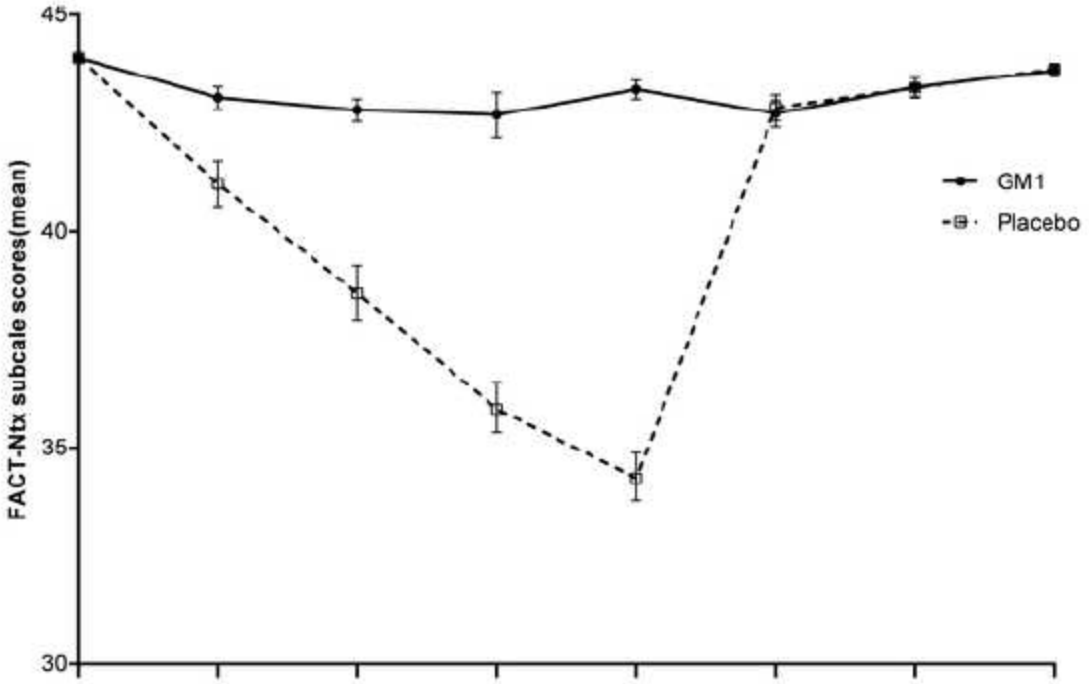
Zhu Y, Yang J, Jiao S*, et al.* Ganglioside-monosialic acid (GM1) prevents oxaliplatin-induced peripheral neurotoxicity in patients with gastrointestinal tumors. World J Surg Oncol 2013;11:19.

Emerging Clinical Trials for the Prevention and Treatment of CIPN

Intervention	Target/Pathway	N	Patient Population
GM-1	Lipid peroxidation inhibition	188	Patients initiating taxane adjuvant therapy

- Recent JNCI publication reported the results in these pts-- randomized to receive GM-1 or placebo
- Dramatic benefit reported

Su Y, Huang Y, Wang S, et al. The effects of ganglioside-monosialic acid in taxane-induced peripheral neurotoxicity in patients with breast cancer: a randomized trial. JNCI. 2019.



	baseline	cycle 1	cycle 2	cycle 3	cycle 4	3 months	6 months	1 year
No. patients								
GM1 group	103	100	100	96	91	89	80	80
Placebo group	103	98	98	97	92	87	79	79

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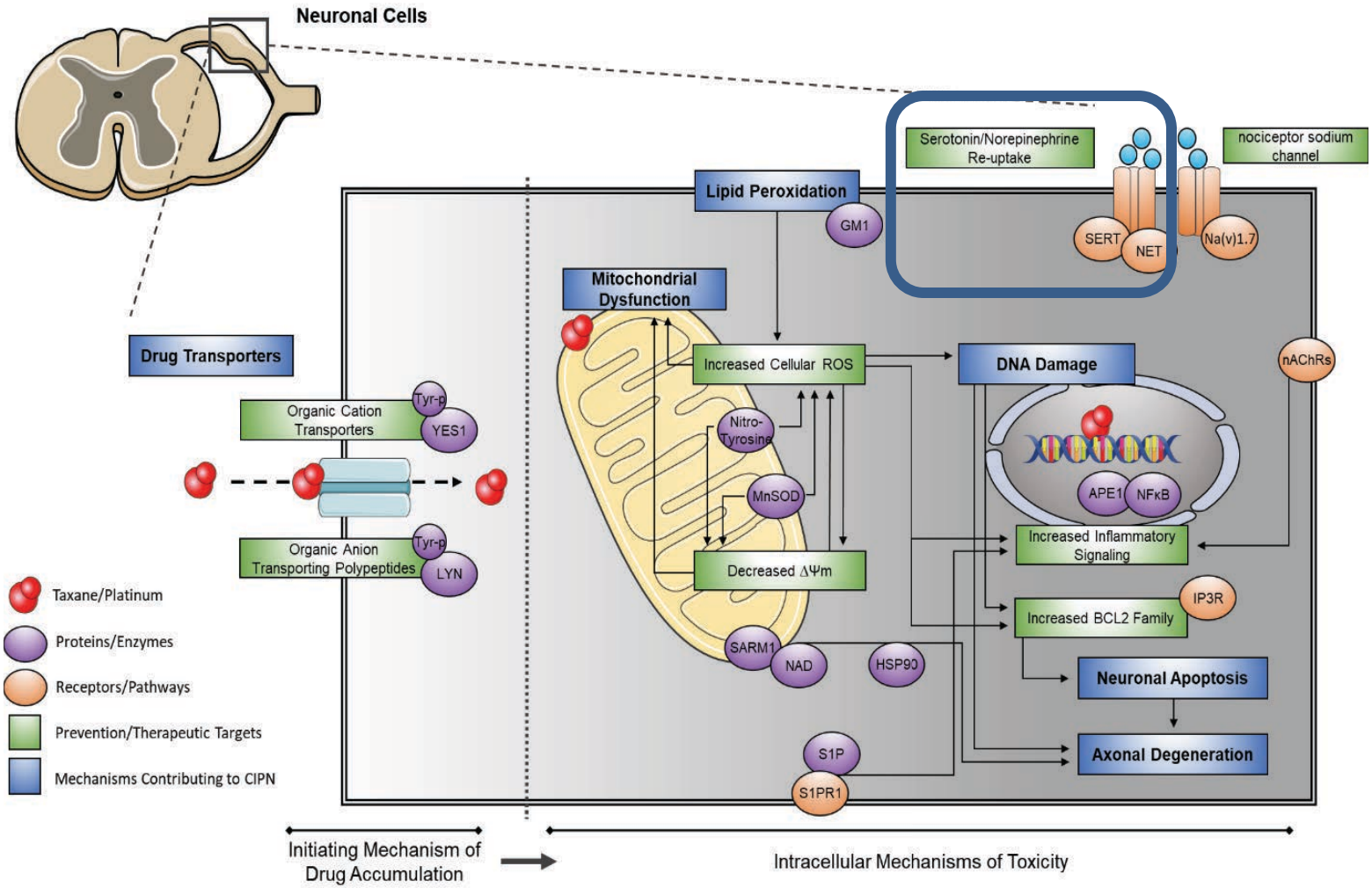
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- Duloxetine, an SNRI, has been the only randomized phase III intervention study in CIPN associated with a significant reduction in established neuropathic pain symptoms
- Proposed mechanisms:
  - Related to the blocking of serotonin and norepinephrine transporters
  - Blocking of sodium channel currents
  - Affecting the descending inhibitory pain neural networks
  - Reducing NF-*k*B and inflammatory responses

Smith EM, Pang H, Cirrincione C*, et al.* Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA 2013;309:1359.

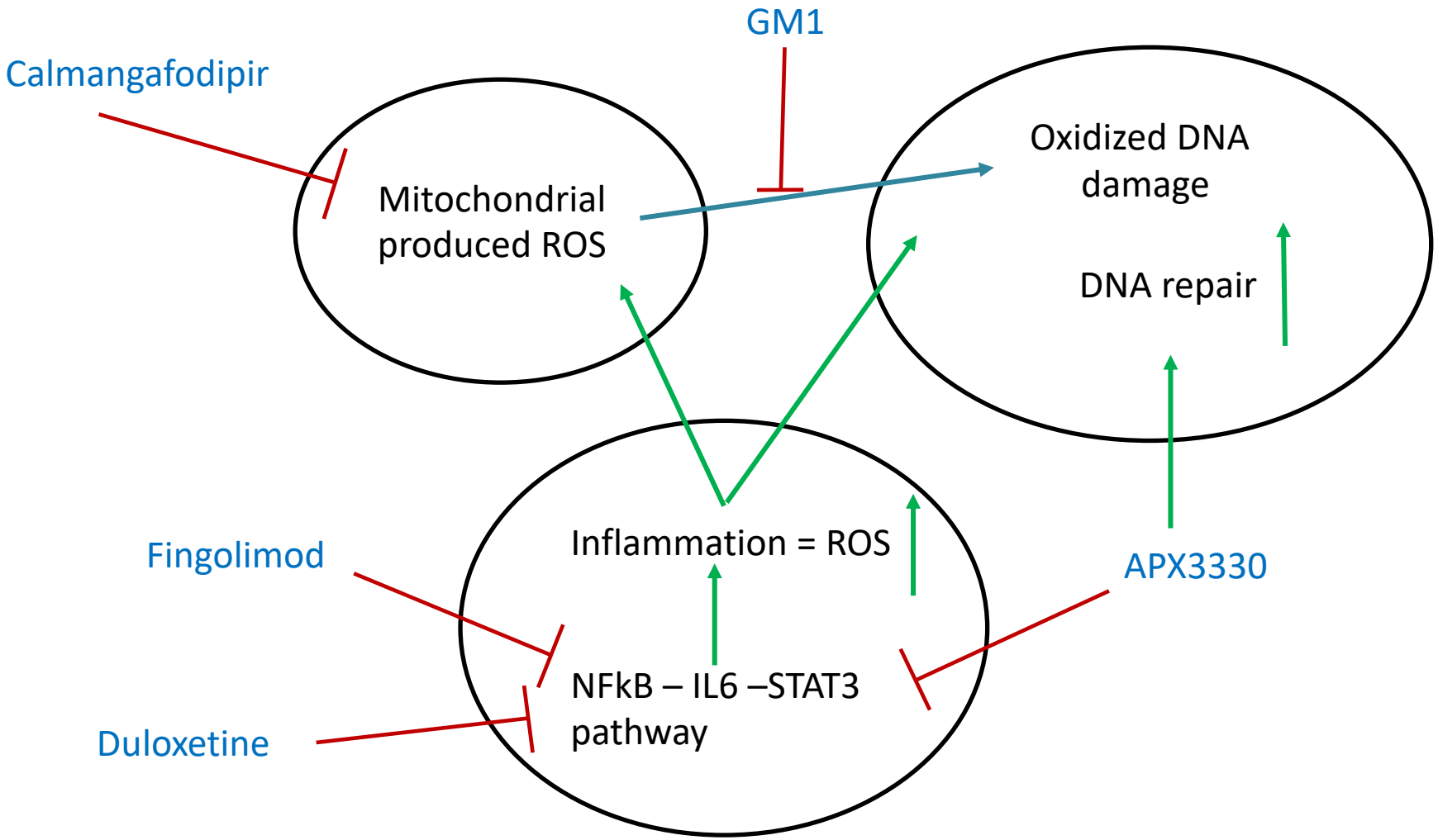
- Emerging preclinical data support that duloxetine may also be effective for prevention of CIPN

- A new NCI-funded clinical trial is currently undergoing protocol development to evaluate the efficacy of duloxetine for prevention of oxaliplatin neuropathy

Emerging Clinical Trials for the Prevention and Treatment of CIPN

Intervention	Target/Pathway	N	Patient Population
Duloxetine	Serotonin-norepinephrine reuptake inhibitor	248	Patients initiating oxaliplatin-based adjuvant therapy

Targeting Inflammation-ROS-Oxidative DNA Damage in CIPN



Conclusions

- CIPN is a big clinical problem
- Better therapy is needed for prevention and or treatment of this problem
- In order to devise better preventive and treatment approaches, mechanisms of CIPN need to continue to be studied
- Neuro-inflammation-ROS-oxidative DNA damage appears to be an important cause of CIPN
- A number of promising, mechanism-based prevention approaches are being evaluated in prospective clinical trials
- Hopefully, such will be successful