Adjuvant Vitamin E and Ovarian Cancer

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Outline

- ➤ Introduction
  - Ovarian Cancer
  - Cisplatin
  - Vitamin E
- ➤ Question
- ➤ Hypothesis
- ➤ Experimental Design
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- ➤ Summary
- ➤ Future Studies

F344 Female Rats

Ovarian Cancer

➢ 5th leading cause of cancer-related deaths in women in the U.S.

- Accounts for about 6% of deaths

➢ Highest mortality rate of gynecologic cancers

➢ Most patients have widespread disease at diagnosis

Cisplatin (CDDP)

➢ Platinum containing chemotherapeutic drug

➢ Highly active against a number of cancers:

- Ovarian, Lung, Cervical, Head & Neck, Testicular

➢ Side effects include:

- Nephrotoxicity, ototoxicity, and **neurotoxicity**

$$Cl_{\cdots}\!\!\diagdown\!\!Pt\!\!\diagup^{\cdots}NH_3$$
$$Cl\diagup\quad\diagdown NH_3$$
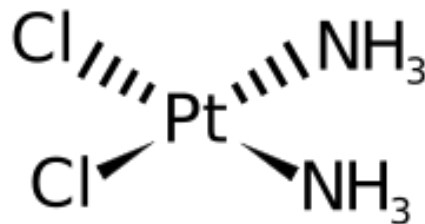
CDDP-Induced Neuropathy (CIPN)

➢ Affects the nerves that carry sensations to the brain

➢ Major dose-limiting adverse side effect of CDDP

➢ Symptoms include:

- Tingling & burning in hands and feet

- Tremors

- Numbness

CDDP-induced Neuropathy & Vitamin E

➢ Mechanism of CIPN is undetermined.

- Platinum accumulation

➢ Clinical and histologic features are similar to those seen in Vitamin E deficiency neuropathy. (Muller '83, Sokol '88)

➢ CDDP decreases plasma Vitamin E in humans. (Weigl '98)

Vitamin E (RRR-α-Tocopherol)

➢ **RRR-α-Tocopherol (α-T):** natural form of vitamin E preferentially retained in the body. (Traber '05)
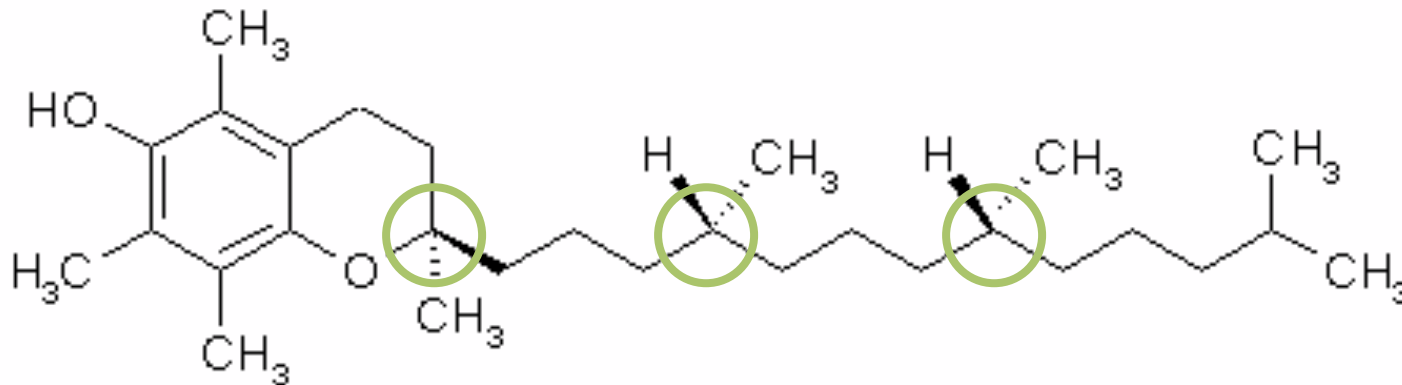
Antioxidant role of α-T

➤ Lipid soluble antioxidant
- Found in cell membranes

➤ Protects cellular lipids from oxidation
- lipid peroxidation

➤ Biomarkers of Lipid peroxidation:
- **F_2-Isoprostanes**
- Malondialdehyde (MDA)

Central Question

Can the neurotoxicity of CDDP be mitigated to allow increased survival without decreased quality of life for ovarian cancer patients?

Central Hypothesis:

1) **CDDP depletes tissue α-T by an oxidative stress mechanism leading to neurotoxicity**

2) **Adjunct α-T will prevent CDDP-mediated α-T depletion, thereby preventing neurologic damage**

3) Adjuvant α-T will not decrease CDDP anti-tumor efficacy

Pre-clinical Model of Ovarian Cancer

Vitamin E (α-T) and Cisplatin (CDDP) Treatment Schedule						
Days:	**Week 1**	**Week 4** (Sun, Tue, Thur)	**Week 5** (Friday)	**Weeks 5-8** (Mon & Thur)	**Weeks 5-8** (Tues & Fri)	**Week 9**
GROUP	TREATMENT					
A Saline	IP inject cells	SC saline	SC saline	SC saline	SC saline	Sacrifice
B α-T	IP inject cells	SC α-T	SC saline	SC α-T	SC saline	Sacrifice
C Cisplatin	IP inject cells	SC saline	SC saline IP CDDP	SC saline	SC saline IP CDDP	Sacrifice
D α-T/ Cisplatin	IP inject cells	SC α-T	SC saline IP CDDP	SC α-T	SC saline IP CDDP	Sacrifice

* Rats treated with CDDP receive an accumulative dose of 18mg / kg
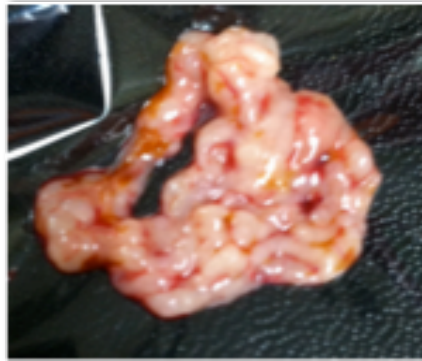
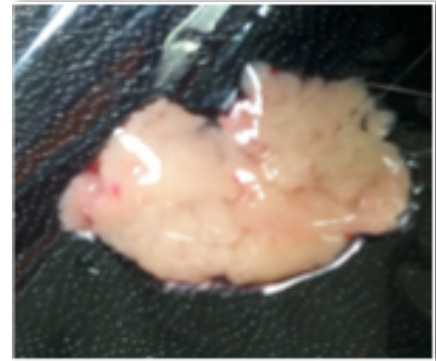# Adjuvant α-T does not alter CDDP-induced weight loss
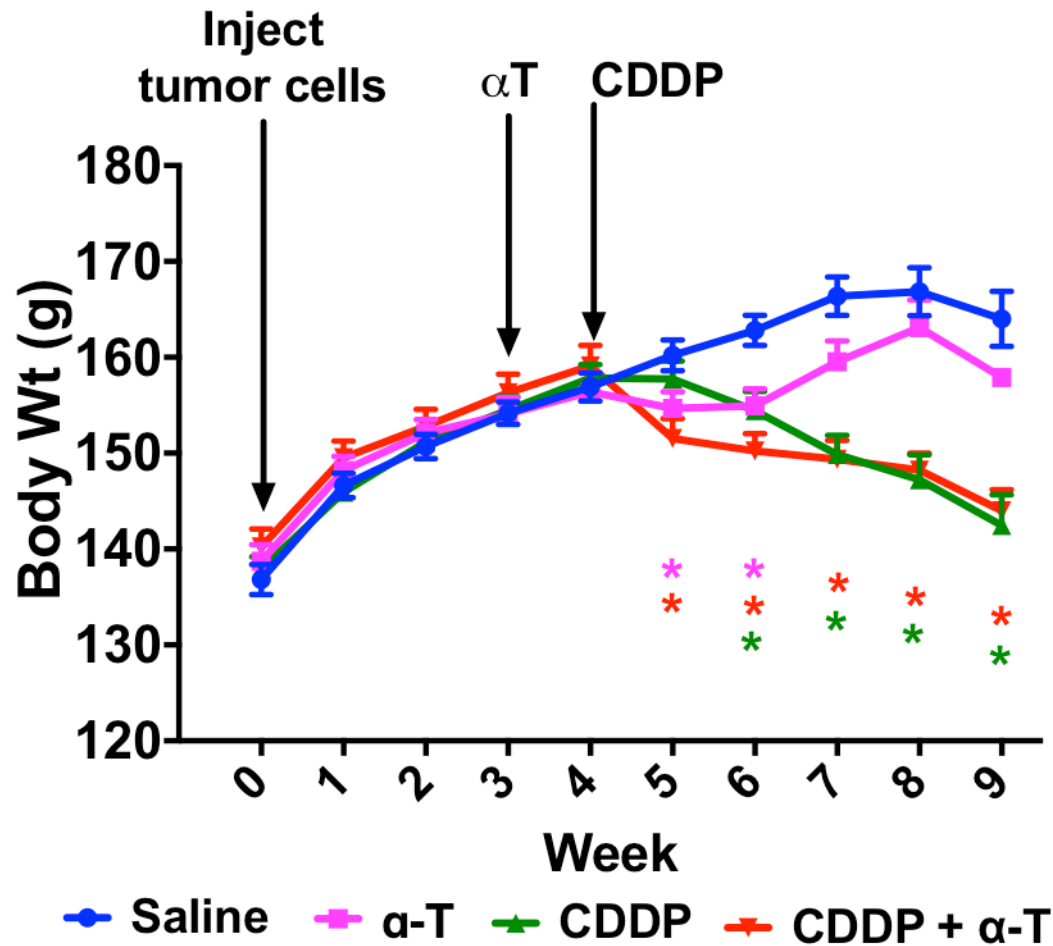
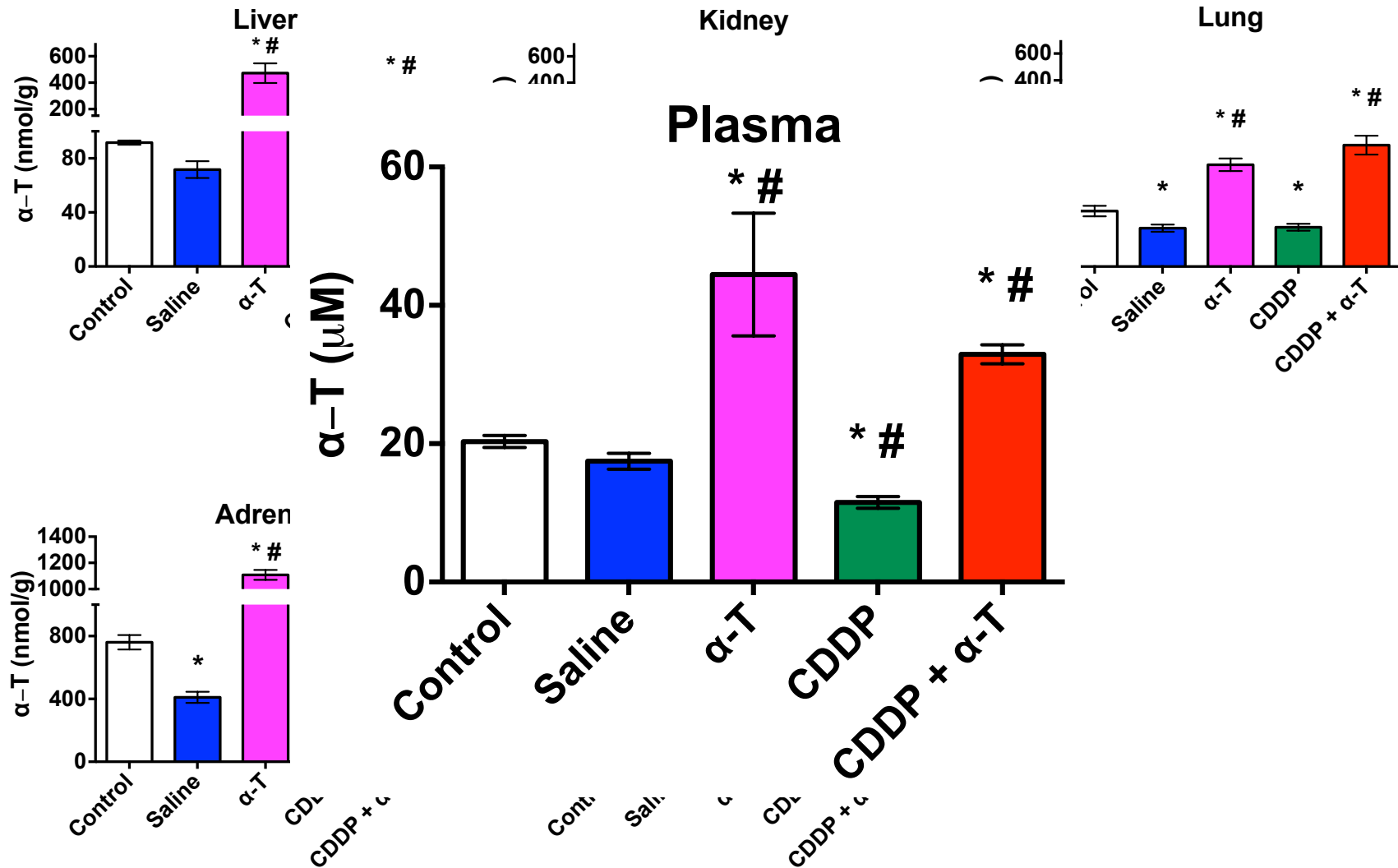# Adjuvant α-T increases CDDP Anti-tumor Efficacy
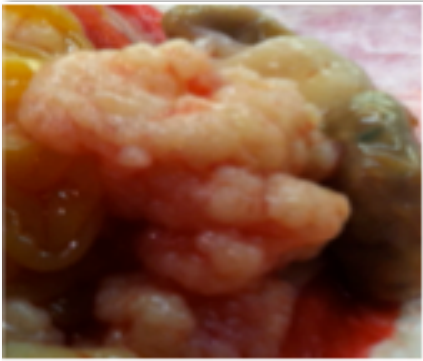
Saline > CDDP > CDDP and α-T

# Adjuvant α-T decreases Tumor Incidence and Multiplicity

| Tumors Per Rat	Number of Rats Per Group				
	0	<10	10-50	50-100	100+
Group A				2/8	6/8
Group B			1/12	8/12	3/12
Group C	2/16	2/16	1/16	8/16	3/16
Group D	10/16	2/16	2/16	1/16	1/16

Adjuvant α-T prevents tumor- and CDDP-induced depletion of α-T
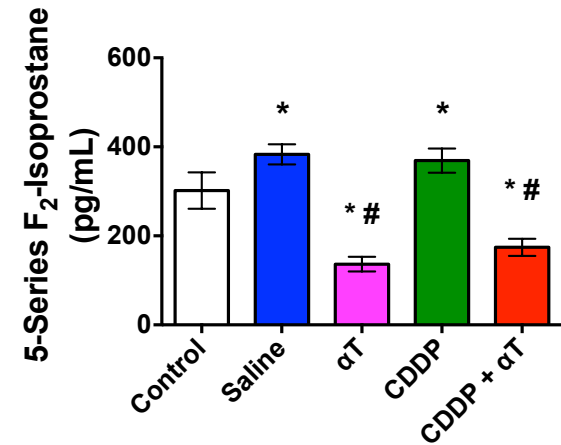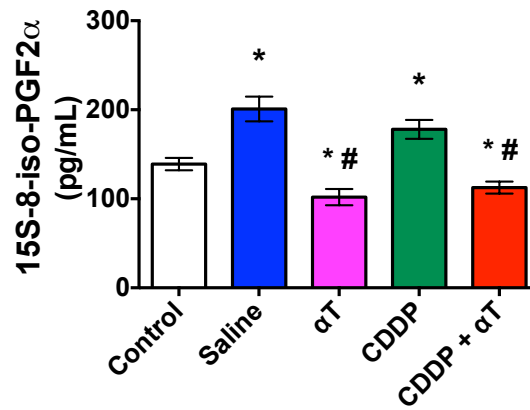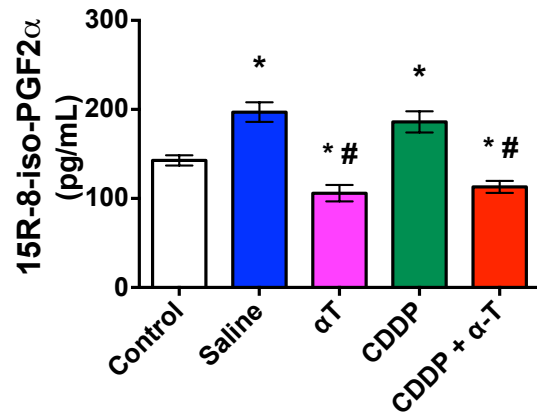

Liver

Kidney

Lung

Plasma

Adren

* = p<0.05 vs. non-tumor controls; # = p<0.05 vs. saline treated tumor-bearing rats

# Adjuvant α-T improves spinal cord α-T levels compared to CDDP alone
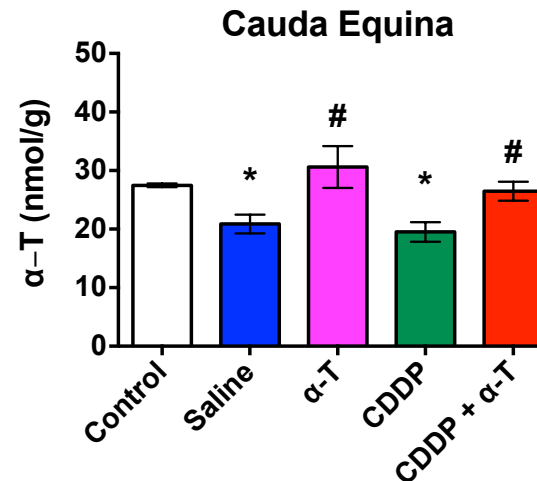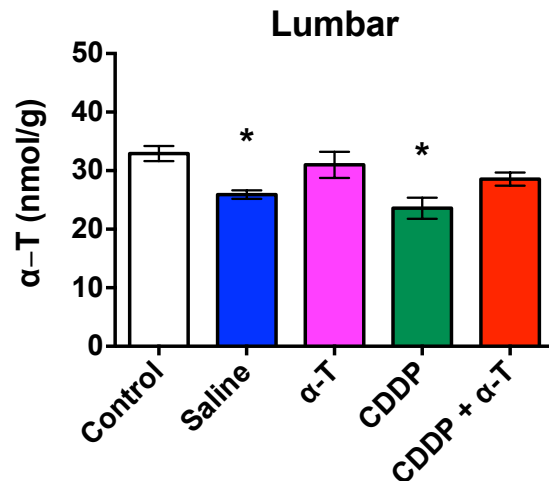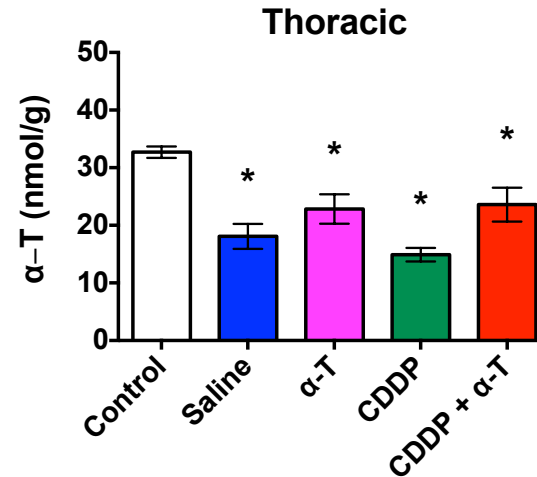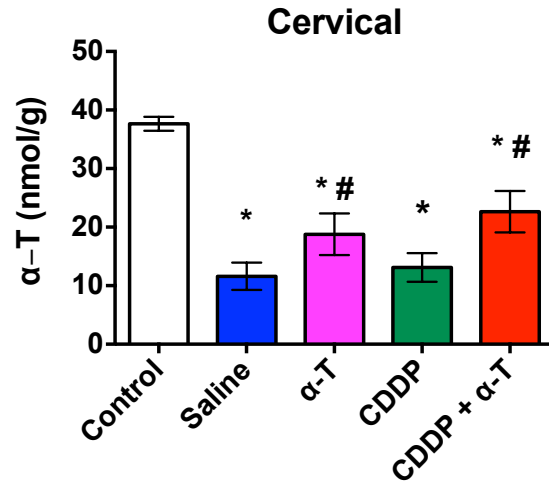
* = p<0.05 compared to non-tumor controls; # = p<0.05 compared to saline treated tumor-bearing rats.

Adjuvant α-T prevents tumor- and CDDP-induced elevation of plasma F$_2$-Isoprostanes

* = p<0.05 compared to non-tumor controls; # = p<0.05 compared to saline treated tumor-bearing rats.

Adjuvant α-T reduces spinal cord and lung platinum but not tumor platinum
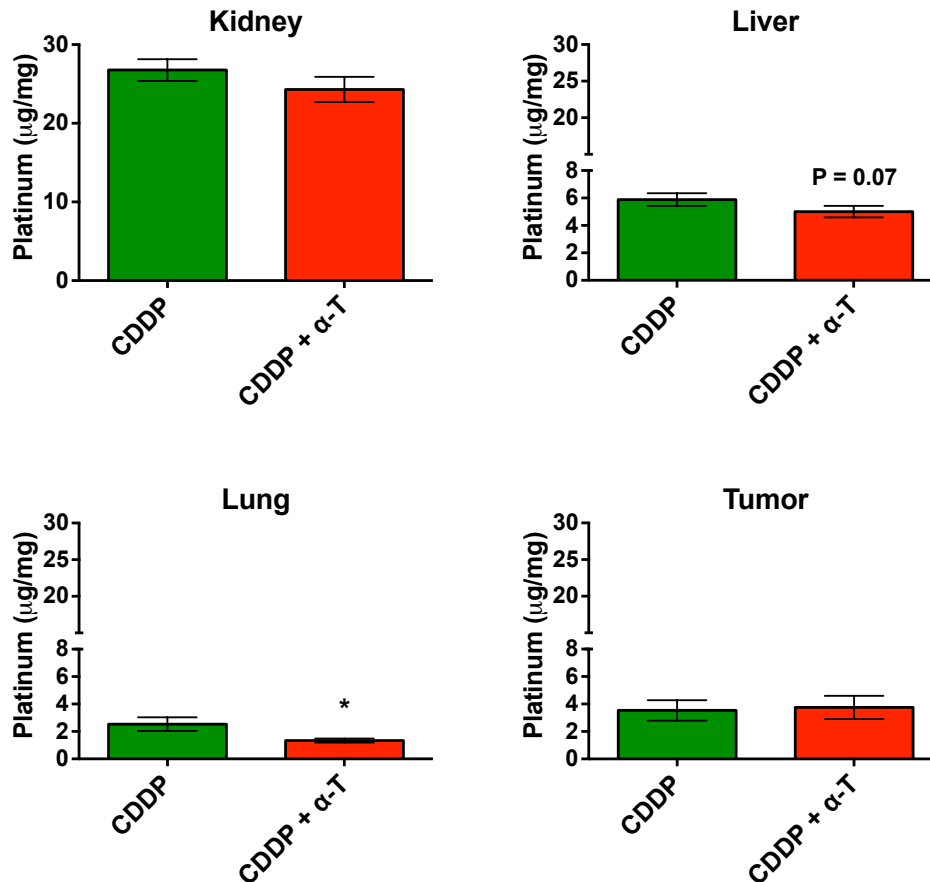
* = p<0.05 compared CDDP alone

Summary

α-T plus CDDP:

➤ Increases CDDP anti-tumor efficacy

  • Decreased tumor burden

➤ Prevents CDDP-induced decreases in tissue and plasma α-T

➤ Prevents tumor- and CDDP-induced lipid peroxidation

➤ Decreases accumulation of platinum in spinal cord tissues but not tumors

Ongoing & Future Studies

Ongoing Studies:

➢Tissue analysis

- MDA – oxidative stress
- Glutathione – antioxidant

➢Histology

- proliferation markers

Future Work:

➢Adjuvant Vitamin C

➢Clinical Trials

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Questions?

Pilot Study in Healthy Rats: CDDP Decreases Ganglia α-T **
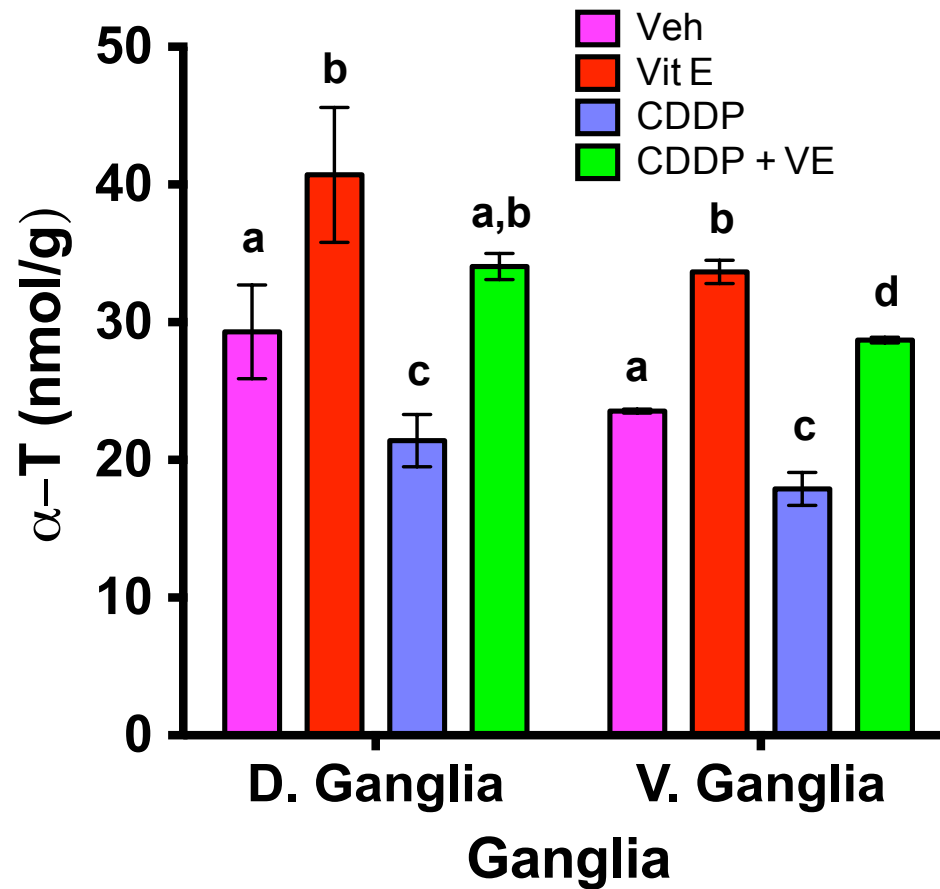
** Columns within the same tissue but with different letter designations are significantly different, p< 0.05
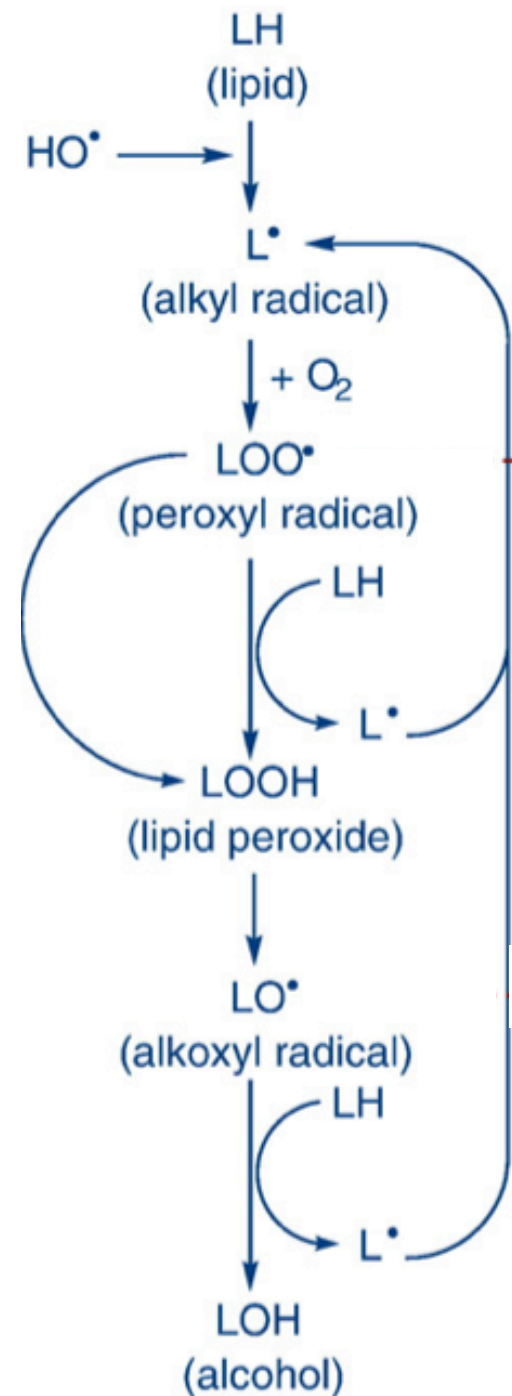
Lipid Peroxidation

1) Initiation
   - Production of a carbon radical

2) Propagation
   - Peroxyl radical and an additional carbon radical are formed

3) Termination
   - Two peroxyl radicals combine to stop the chain reaction

F$_2$-Isoprostane from Arachidonic Acid

5-series IsoP 12-series IsoP 8-series IsoP 15-series IsoP