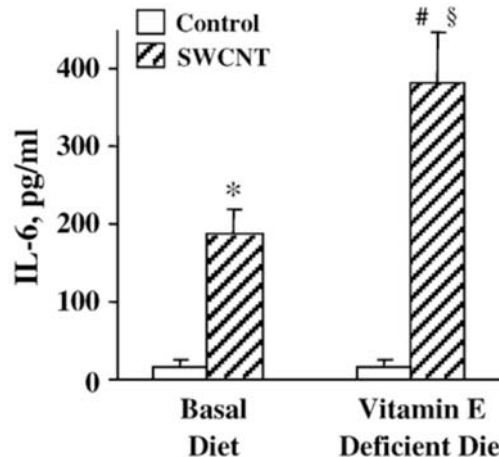
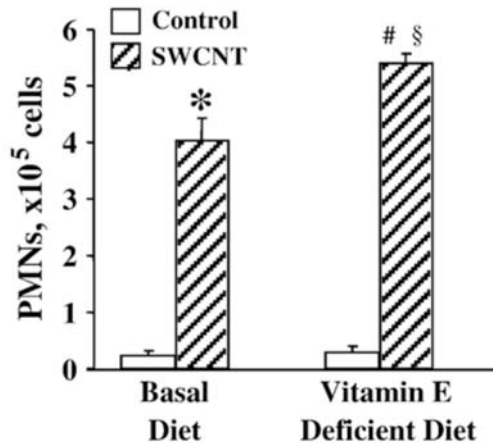
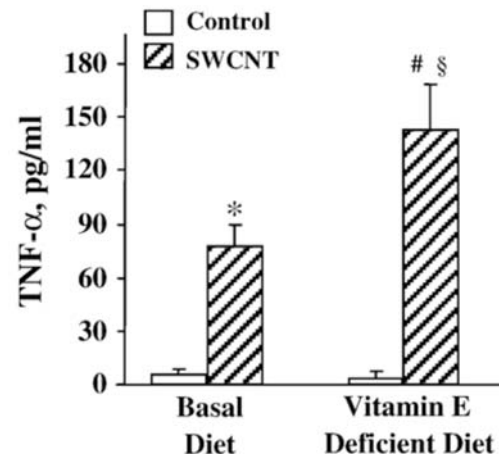
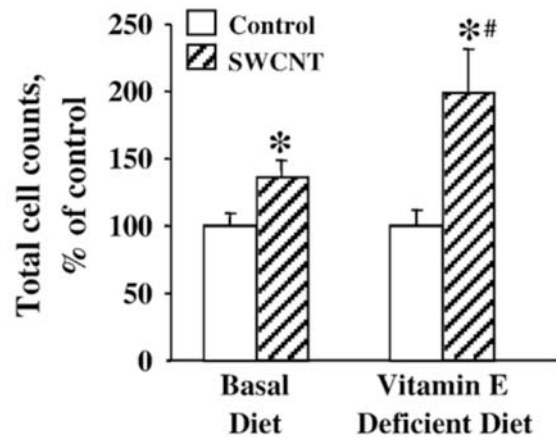


*OXIDANTS* as a mechanism of action ?

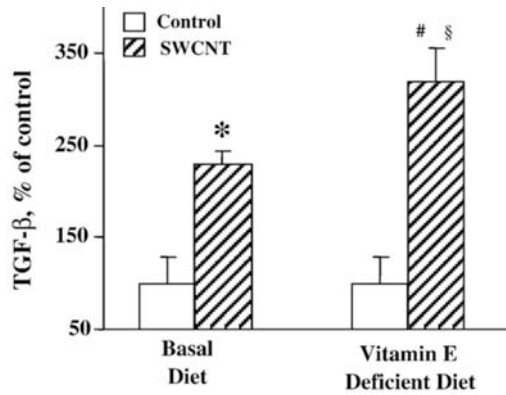
C57Bl/6 mice on a Vitamin E-deficient diet for 24 weeks, and further exposed to 40  $\mu\text{g}$  SWCNT by (<2% iron) pharyngeal aspiration – 24 hours time point



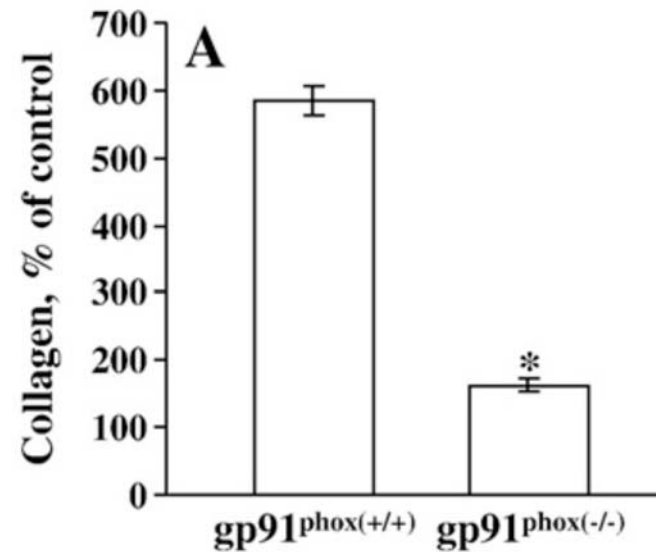
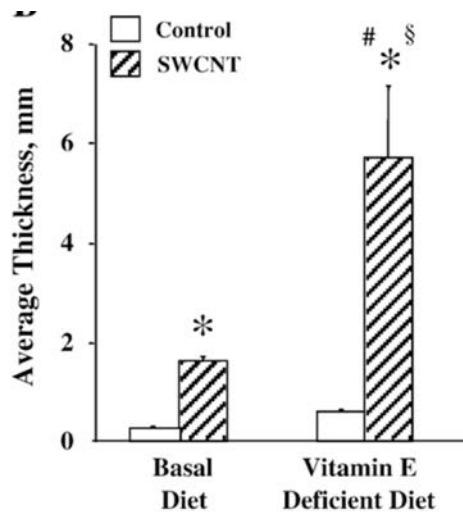
**Oxidants** play a role in CNT-induced pulmonary inflammation

*OXIDANTS* as a mechanism of action ?

C57Bl/6 mice on a Vitamin E-deficient diet for 24 weeks, and further exposed to 40  $\mu$ g SWCNT by pharyngeal aspiration – 28 days time point



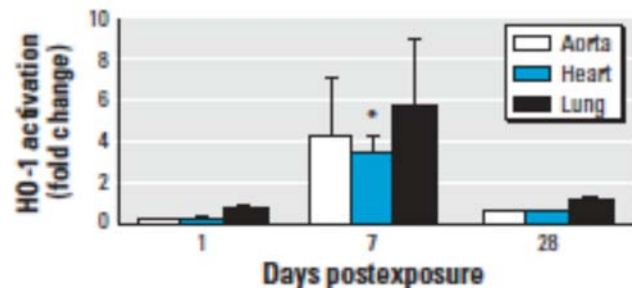
**Oxidants** play a role in CNT-induced pulmonary **fibrosis**



NADPH oxidase (-/-) mice exposed to 40  $\mu$ g SWCNT by pharyngeal aspiration for 28 days

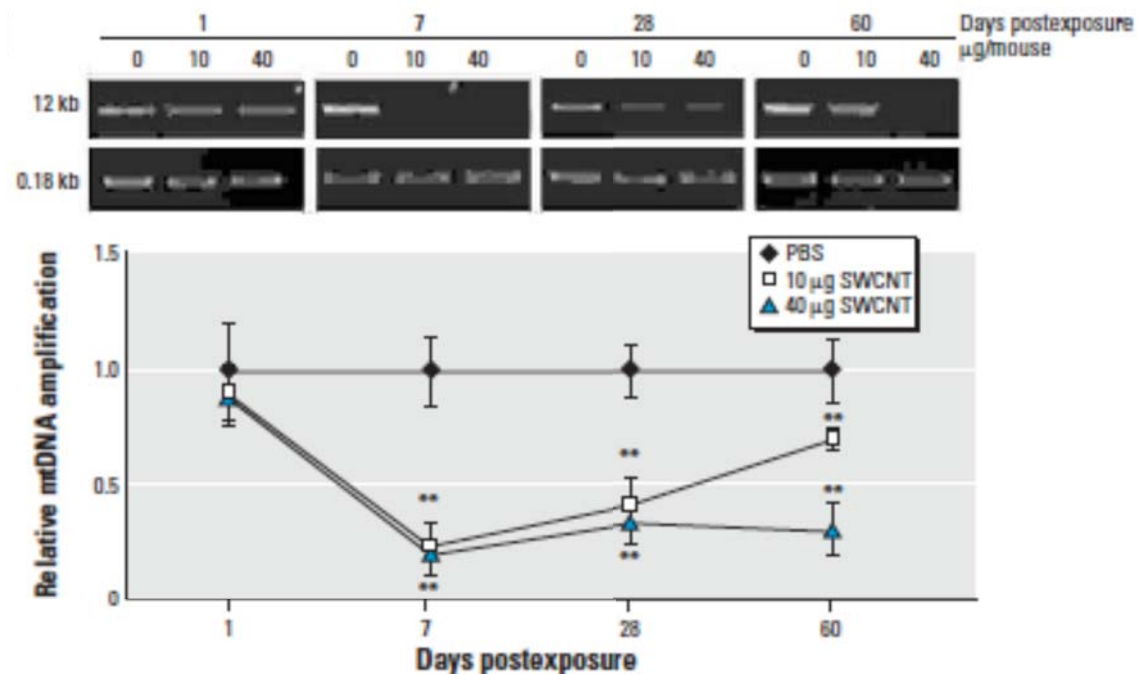
*SYSTEMIC effects* as a mechanism of action ?

C57Bl/6 mice exposed to 10 or 40  $\mu\text{g}$  SWCNT (<2% iron) by pharyngeal aspiration up to 60 days



*HO1-Luc mice*

*Li et al Environ. Health Perspect. 115 (2007) 377-382*



*Aortic mitochondrial damage*

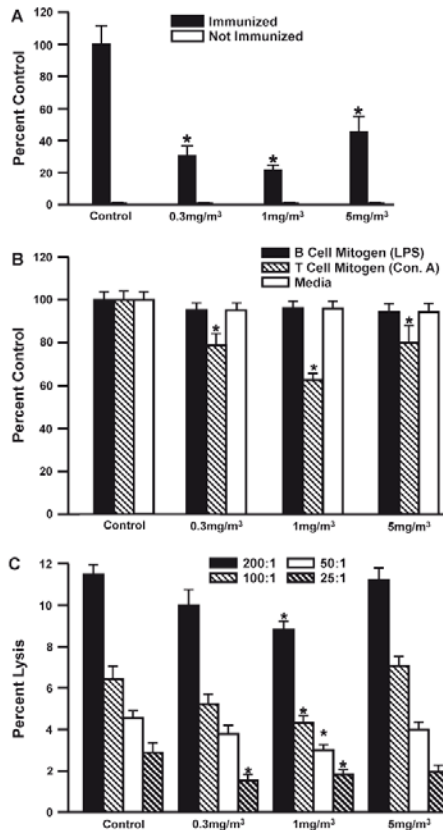


**Pulmonary administration of CNT induces systemic effects**

*SYSTEMIC effects* as a mechanism of action ?

C57Bl/6 mice exposed to 0.3-5 mg/m<sup>3</sup> MWCNT by inhalation (6 hours/day) for 14 days

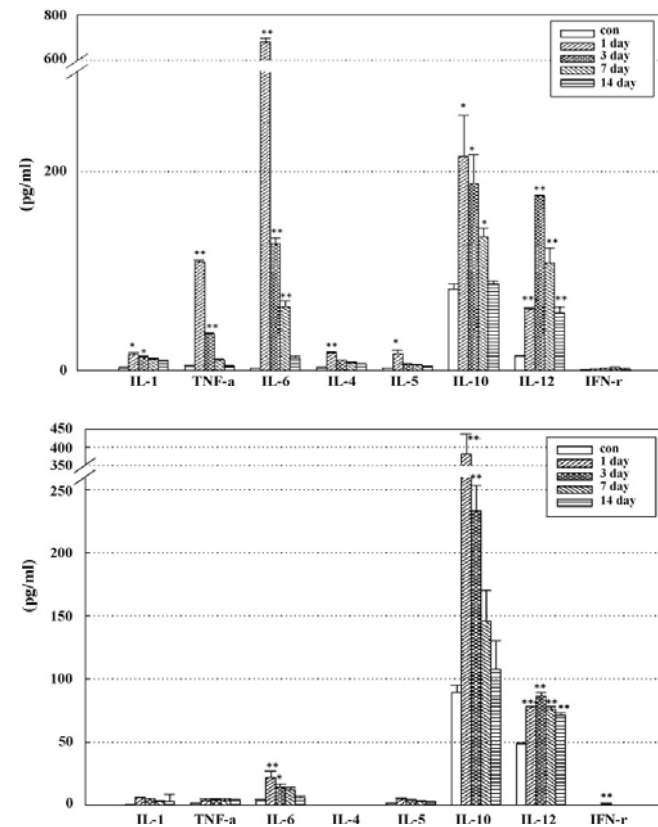
ICR mice exposed to 5-50 mg/kg MWCNT by intratracheal instillation – up to 14 days



=> Alteration of T cells function

=> Alteration of innate immunity (NK cells)

Mitchell et al. *Toxicol. Sci.* 100 (2007) 203-214  
Mitchell et al. *Nature Nano.* 4 (2009) 451-456



=> Production of cytokines in the BAL

=> Production of cytokines in the blood

Park et al. *Toxicology* 259 (2009) 113-121



**Pulmonary administration of CNT induces systemic effects**

# Biopersistence

Rats exposed to MWCNT by intratracheal instillation for 60 days

Single i.t. dose	Time after particle administration		
	Day 0	Day 28	Day 60
NaCl 0.9%	ND <sup>a</sup>	ND <sup>a</sup>	ND <sup>a</sup>
	0.4 ± 0.1 <sup>b</sup>	0.3 ± 0.1 <sup>b</sup>	0.4 ± 0.1 <sup>b</sup>
0.5 mg CNT		(78.4% ± 15.3) <sup>c</sup>	(81.2% ± 26.4) <sup>c</sup>
	0.5 ± 0.1 <sup>b</sup>	0.4 ± 0.1 <sup>b</sup>	0.2 ± 0.1 <sup>b</sup>
0.5 mg ground CNT		(78.4% ± 12.4) <sup>c</sup>	(36.0% ± 13.2) <sup>c</sup>

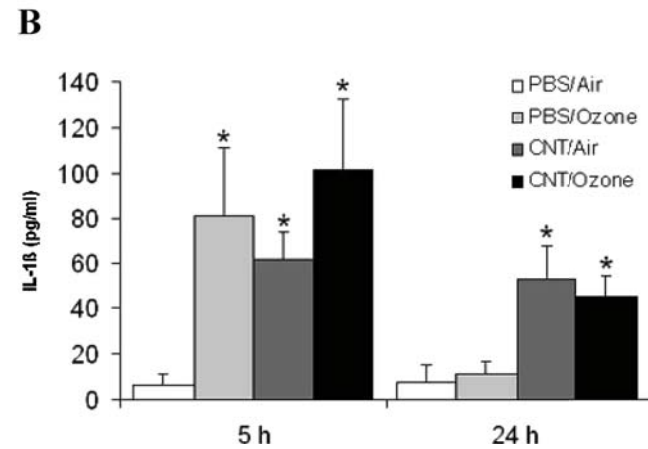
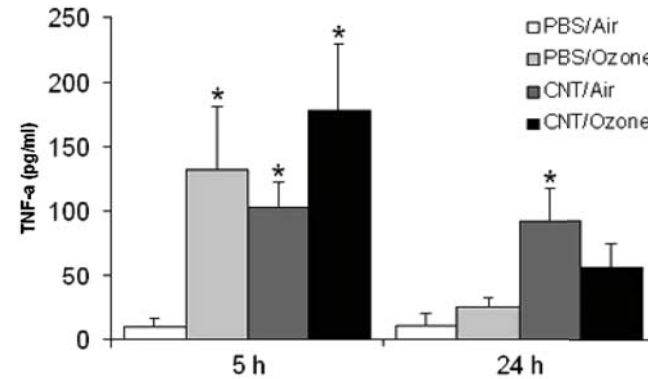
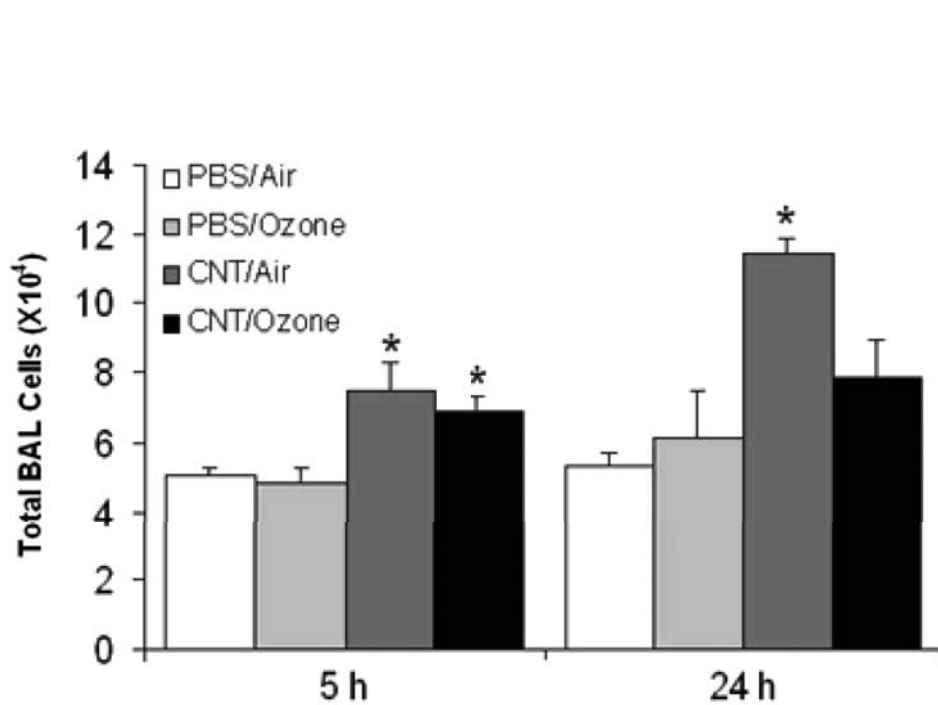
*Muller et al Toxicol. Applied Pharmacol. 207(2005) 221-231*

Similar results obtained up to 6 months after intratracheal administration of 100 µg MWCNT to rats

*Elgrabli et al Part. Fiber Toxicol. 5 (2008) 20*

**AMPLIFICATION** of an existing pathology ?

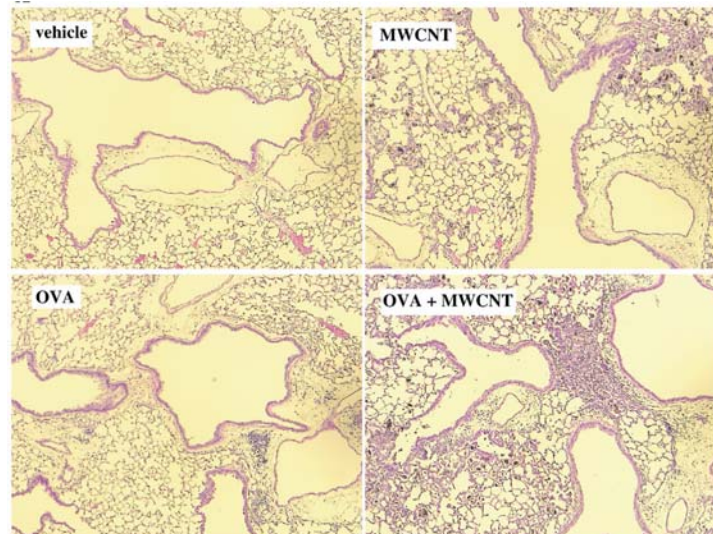
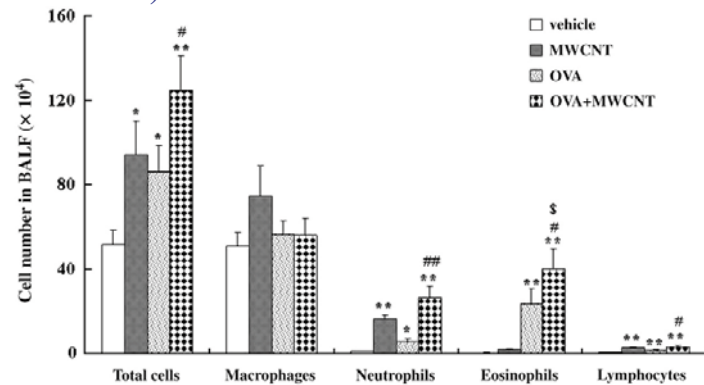
C57Bl/6 mice exposed to 20 µg MWCNT by pharyngeal aspiration +/- 0.5ppm ozone for 4 hrs



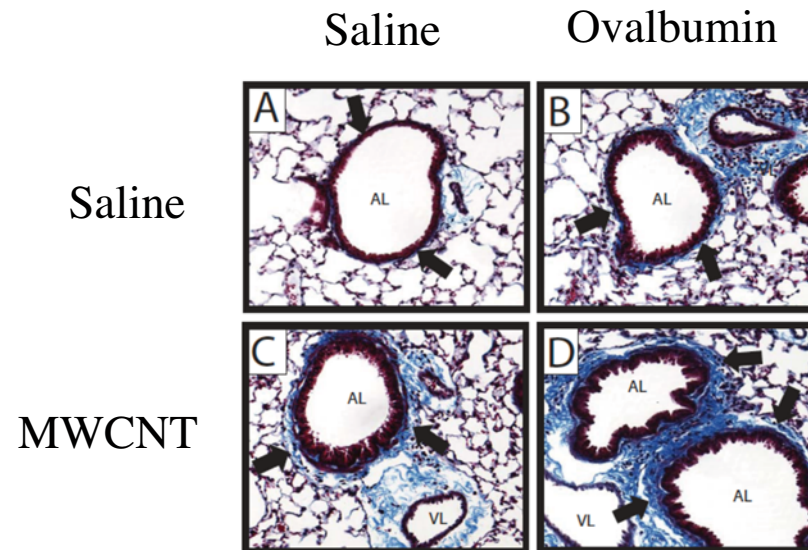
**No synergistic effects of CNT with ozone**

# AMPLIFICATION of an existing pathology ?

50 µg MWCNT by intratracheal instillation in a model of asthmatic mice (j-14 and j-7 OVA ip, j-1 OVA inhal, j0 MWCNT inhal, evaluation **24 hours** post exposure to MWCNT)



100 mg/m<sup>3</sup> MWCNT by inhalation in a model of asthmatic mice (j-14 and j-7 OVA ip, j-1 OVA inhal, j0 MWCNT inhal, evaluation **14 days** post exposure to MWCNT)

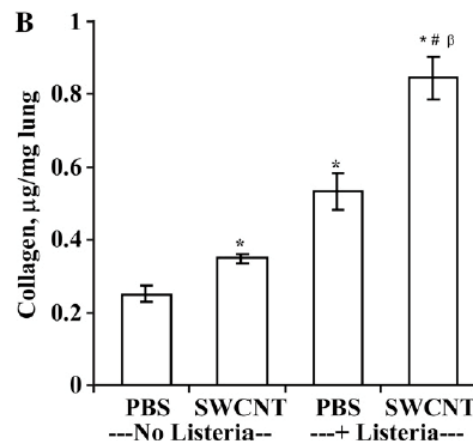
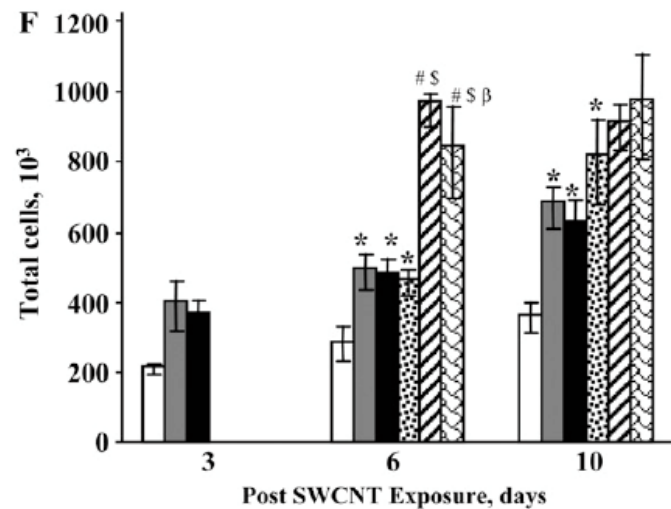
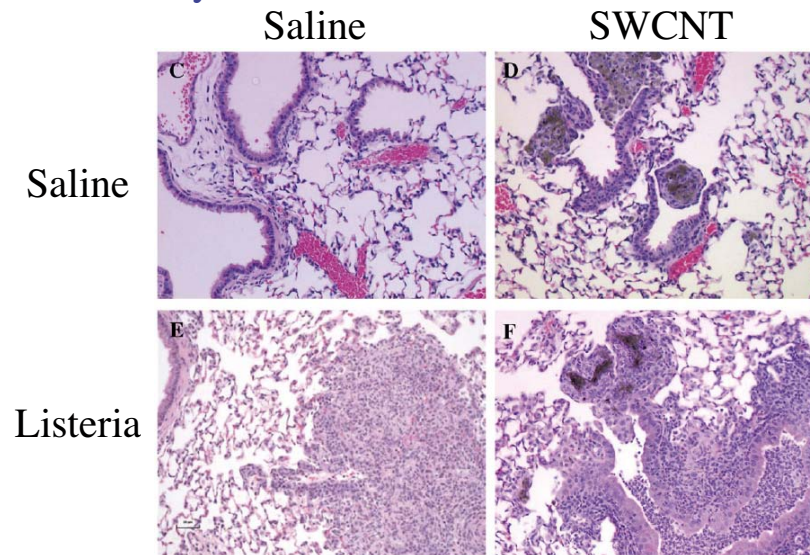
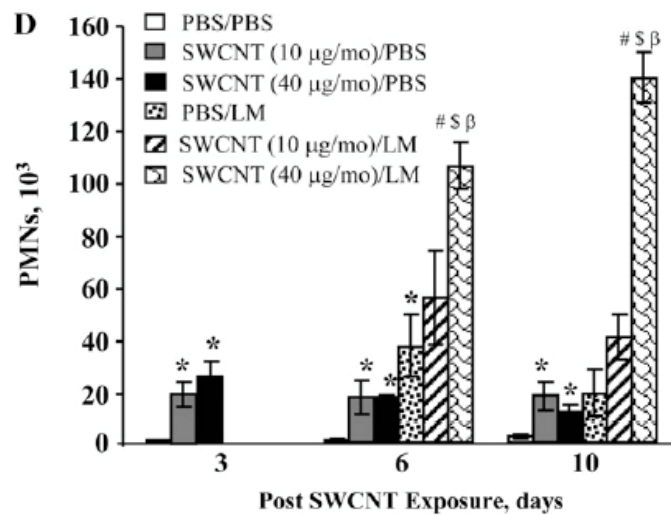


**MWCNT potentialize early inflammation and late fibrosis in asthmatic mice**

*Inoue et al Toxicol. Appl. Pharmacol. 237 (2009) 306-316*

# AMPLIFICATION of an existing pathology ?

10 or 40µg/mice SWCNT by pharyngeal aspiration, and Listeria at day 3



**SWCNT**  
potentiate bacterial  
(Gram +) infection

## Actual knowledge - remaining uncertainties

### KNOWLEDGE

Exposure of animals to Carbon Nanotubes leads to:

- Inflammatory response (transitory, neutrophils)
- Granuloma
- Fibrosis

### UNCERTAINTIES

What are the determinants of CNT effects ?

- Physico-chemical properties (# walls, length, catalyst, dispersion, functionalization, ...)
- Route of exposure
- Oxidative properties
- ... ?

# Aknowledgments

**Laboratoire Francis Perrin, CEA, Saclay:**  
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