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Deficient macrophage autophagy protects mice from CeO_2 nanoparticle-induced alveolar remodeling

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Connaissance - Action

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Serenade
Safe(r) Ecodesign Research and Education applied to nAnomaterial DEvelopment.

- CeO_2 are used as diesel fuel catalyst to reduce emissions of particulate matter ➔ emission of CeO_2 nanoparticles (NP)

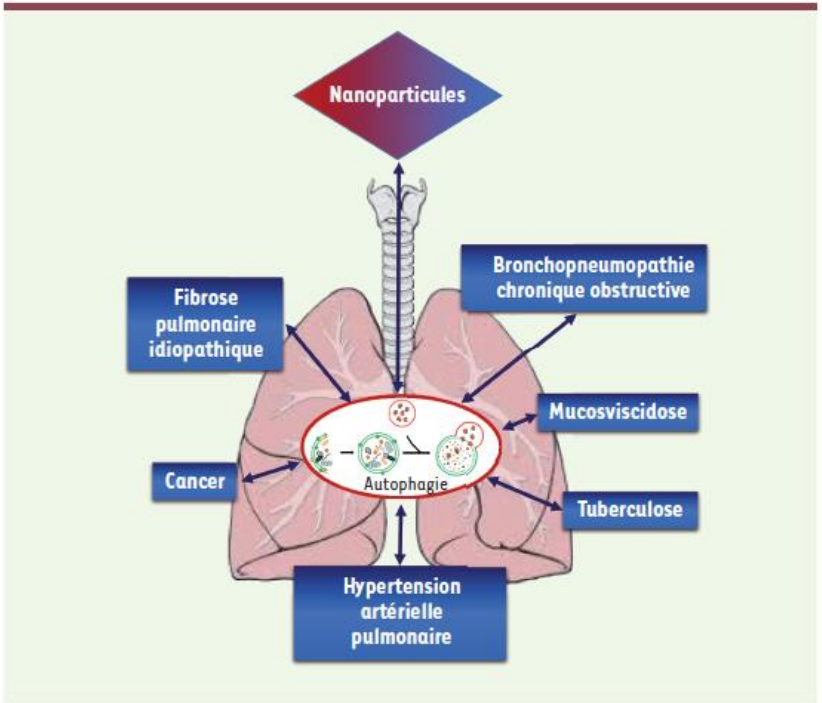
- Pulmonary exposure to CeO_2 NP
  - ➔ Granuloma formation
  - ➔ Lung remodeling (fibrosis)

Ma et al. Toxicol Appl. Pharmacol. ***2012***
Ma et al. Toxicol Appl. Pharmacol. ***2014***

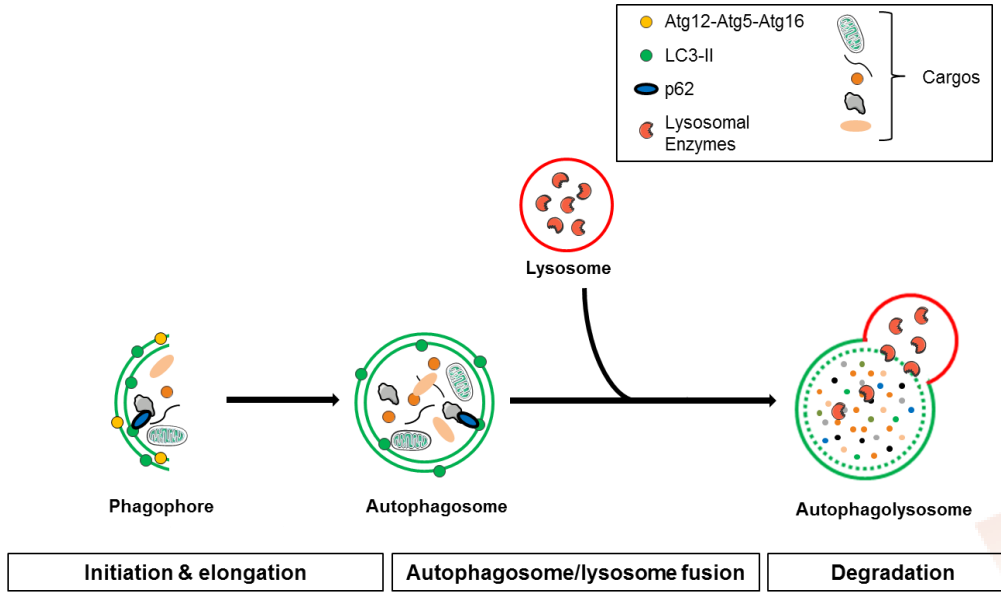
- Exact underlying mechanism?
  - ➔ Epithelio-mesenchymal transition
  - ➔ Autophagy?

Hussain et al. ACS Nano ***2012***
Ma et al. Toxicol Appl. Pharmacol. ***2017***
Aalapati et al. Nanotoxicology ***2017***

- A self-eating physiological process
- Role in health and diseases



Lanone et al. Med&Sci. ***2017***



Adapted from Cohignac et al. Nanomaterials ***2015***

- Modulated, in macrophages, in response to NP, depending on their physico-chemical characteristics

Cohignac et al. Autophagy ***2018***

Hypothesis:

Lung remodeling induced by pulmonary exposure to CeO_2 NP could be linked to modifications of autophagy

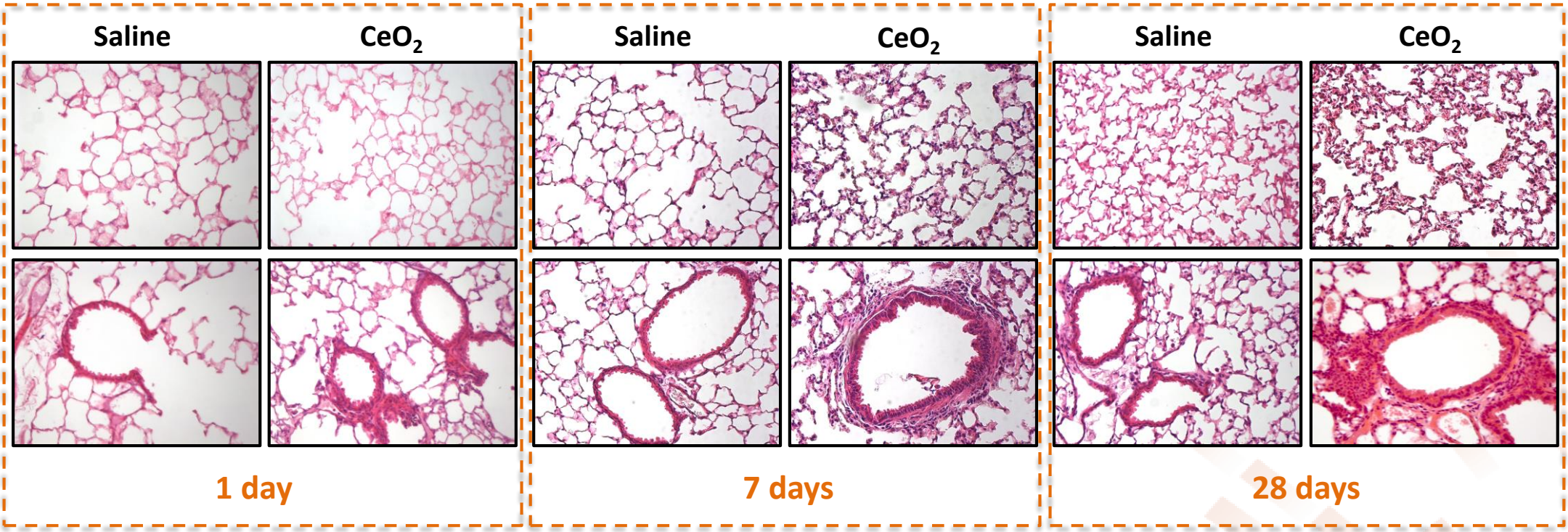
Objectives:

- Characterize **lung remodeling** in response to CeO_2 NP
- Evaluate the **contribution of macrophagic autophagy** in this response

Pulmonary exposure to CeO2 NP: induction of lung remodeling?

Oropharyngeal aspiration of saline of 50µg CeO_2 NP
Sacrifice 24h, 1 week or 28 days later

HES

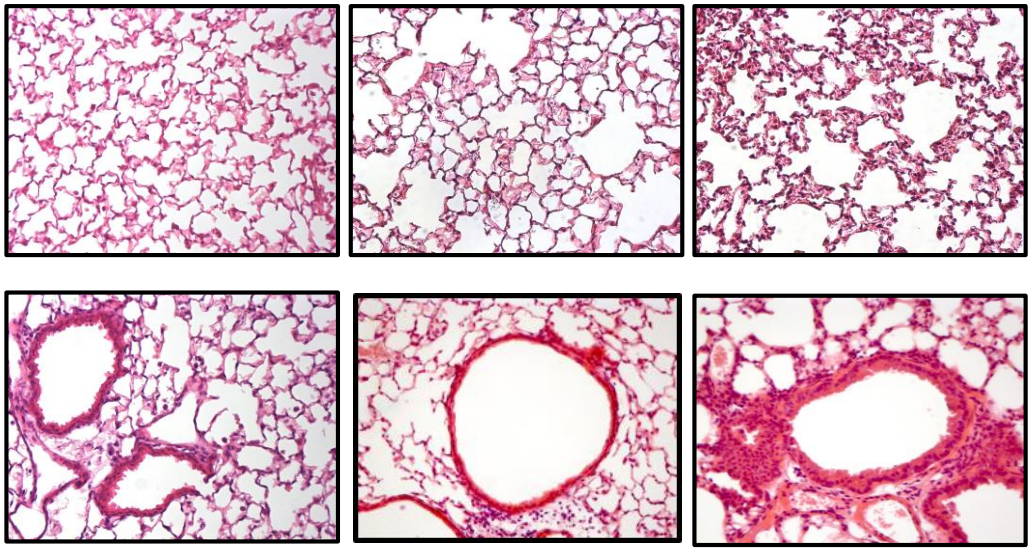


- Progressive **perialveolar** and **peribronchial thickening** after single oropharyngeal administration of **CeO_2 NP**

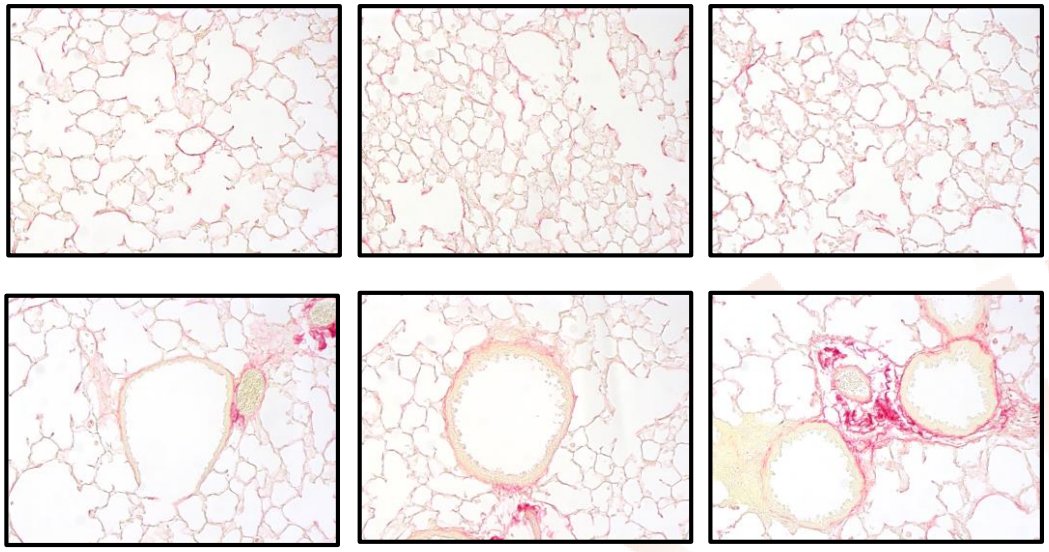
Pulmonary exposure to CeO2 NP: induction of lung remodeling?

Oropharyngeal aspiration of saline of 5 or 50µg CeO_2 NP
Sacrifice 28 days later

HES



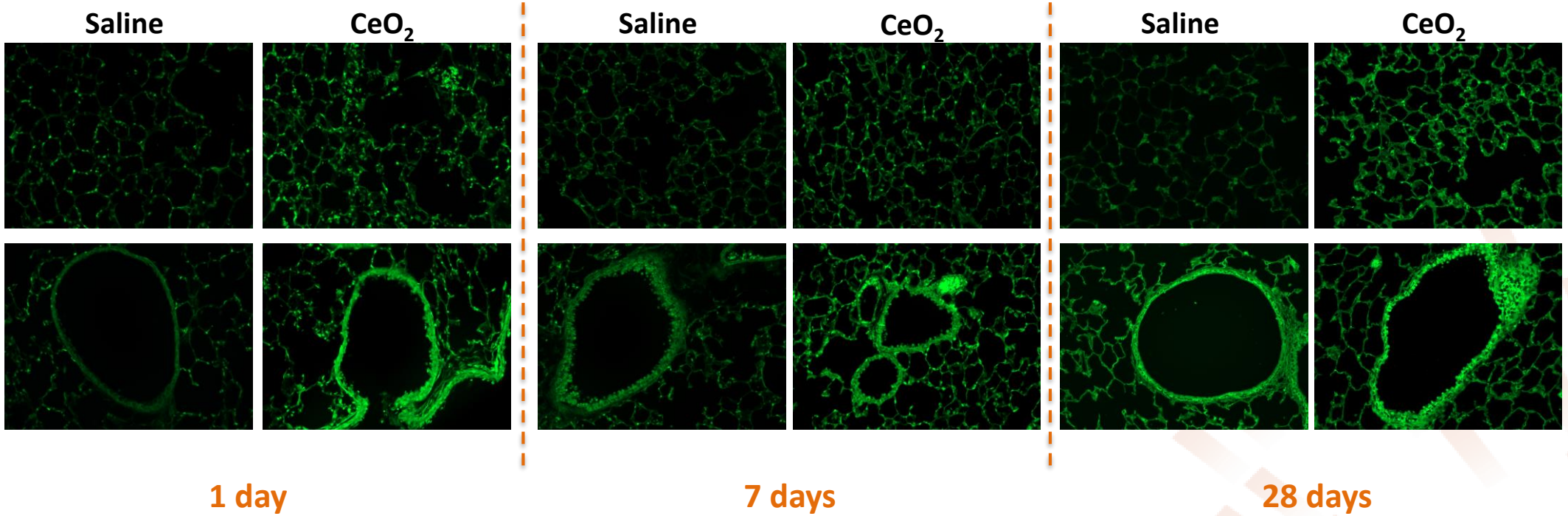
Sirius red



- Dose-dependent **perialveolar** and **peribronchial thickening** after single oropharyngeal administration of **CeO_2 NP**

Pulmonary exposure to CeO2 NP: induction of autophagy?

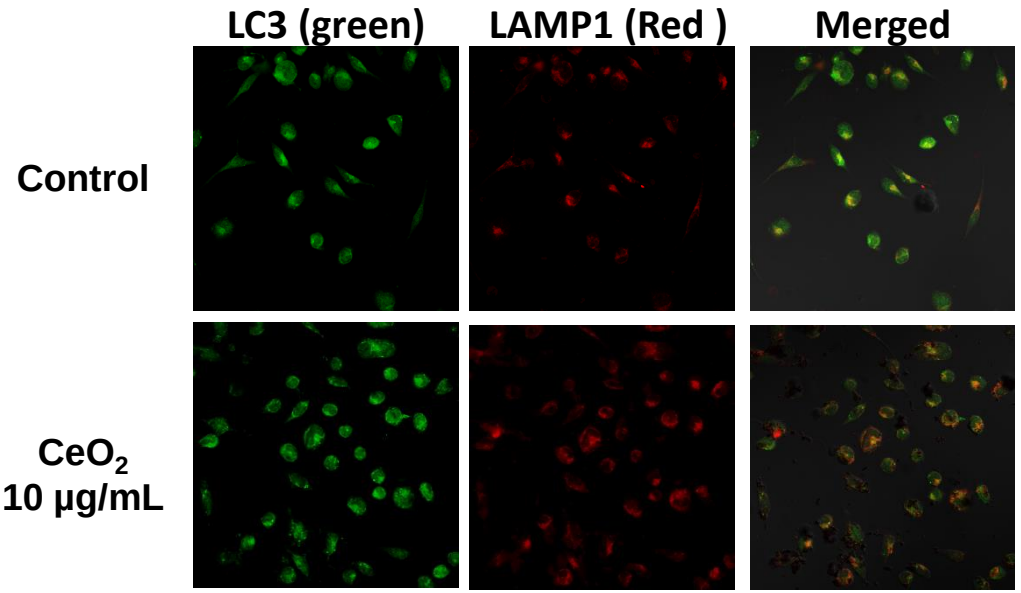
Oropharyngeal aspiration of saline of 50µg CeO_2 NP
Sacrifice 24h, 1 week or 28 days later
GFP-LC3 mice



- Activation of **(macrophagic) autophagy** after single oropharyngeal administration of **CeO_2 NP**

Macrophage exposure to CeO_2 NP: activation of autophagy?

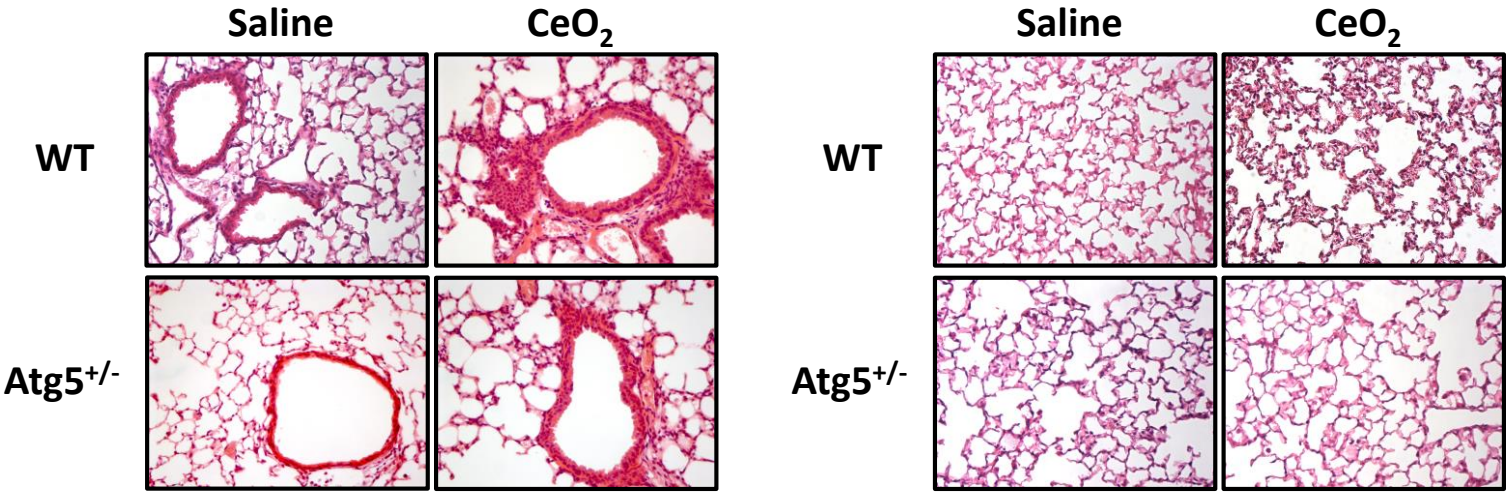
Peritoneal macrophages (GFP-LC3 mice) exposed to 10µg/ml CeO_2 NP
*LC3 (green): **Autophagosome**; LAMP1 (red): **lysosome**; merged (orange): **autolysosome***

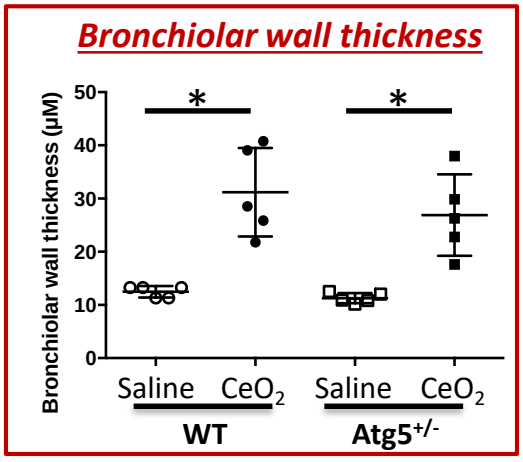


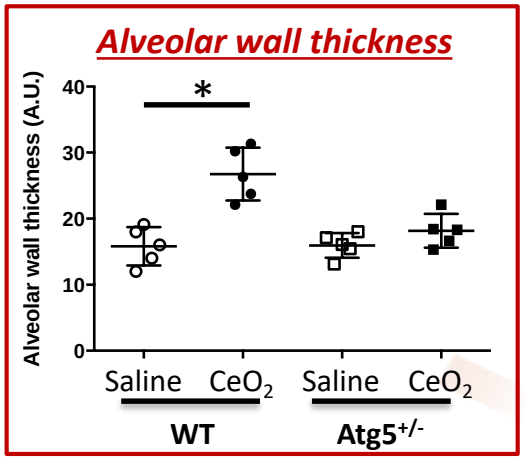
- **Macrophage** exposure to **CeO_2 NP** induces a **functional autophagy**

Deficient macrophagic autophagy: protection from remodeling in response to CeO_2 NP?

Oropharyngeal aspiration of saline of 50µg CeO_2 NP - Sacrifice 28 days later
$Atg5^{flox}LysM^{Cre}$ mice ➔ ***inactivation of macrophagic autophagy***



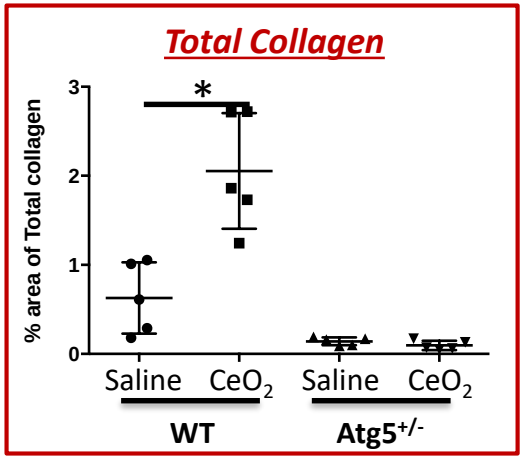


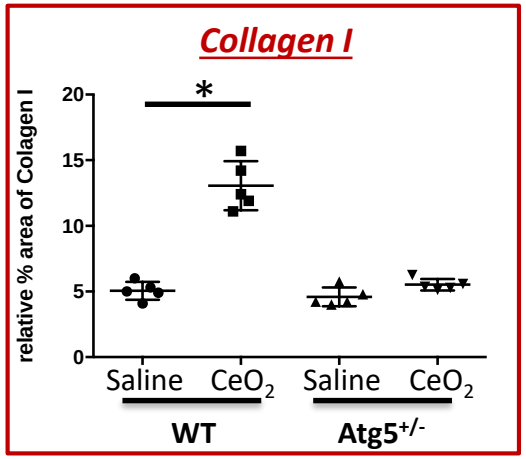


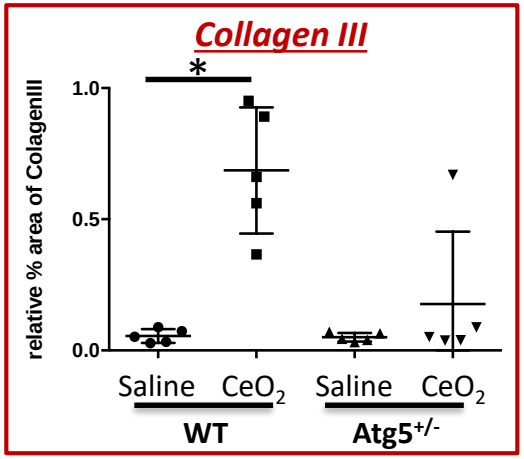
- **Deletion** of autophagy in **macrophages** ➔ **protection** against **alveolar** but **not bronchiolar** remodeling after single oropharyngeal administration of **CeO_2 NP**

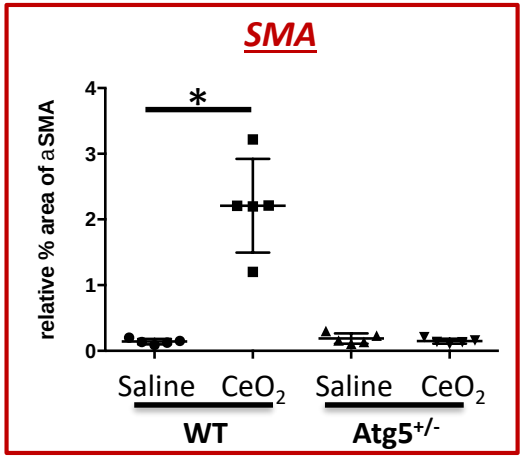
Deficient macrophagic autophagy: protection from remodeling in response to CeO_2 NP?

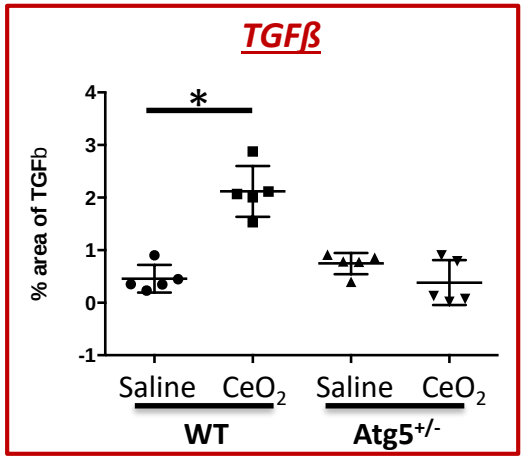
Oropharyngeal aspiration of saline of 50µg CeO_2 NP - Sacrifice 28 days later
$Atg5^{flox}LysM^{Cre}$ mice ➔ ***inactivation of macrophagic autophagy***









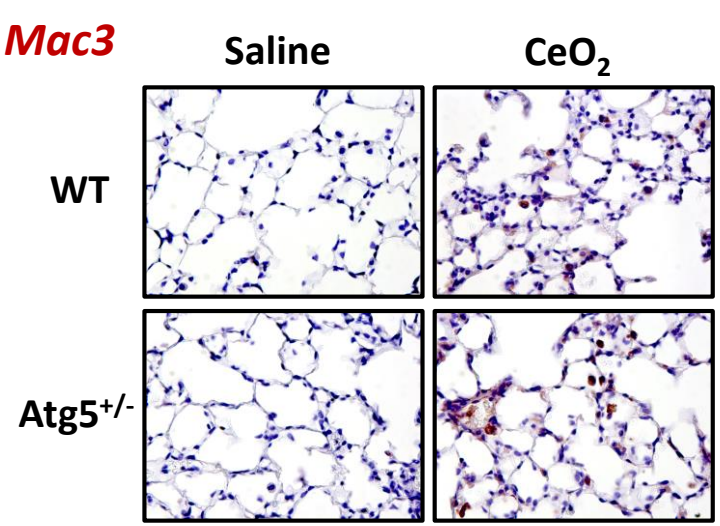


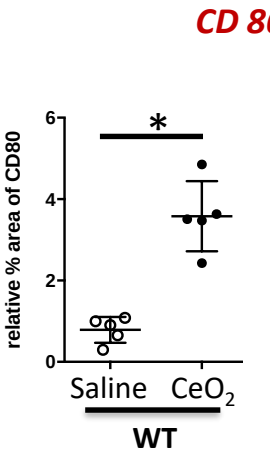
- **Deletion** of autophagy in **macrophages** ➔ **protection** against **alveolar remodeling** after single oropharyngeal administration of **CeO_2 NP**

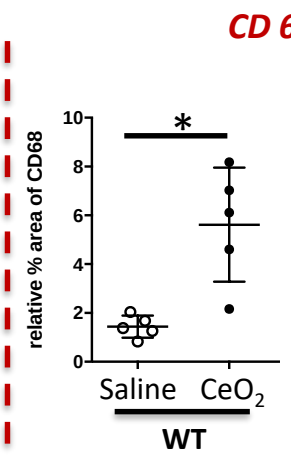
Mechanism of protection: modification of M1/M2 balance?

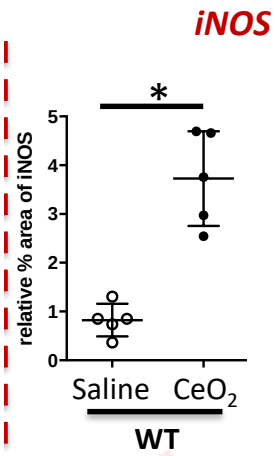
Oropharyngeal aspiration of saline of 50µg CeO_2 NP - Sacrifice 28 days later

Quantification/qualification of macrophages



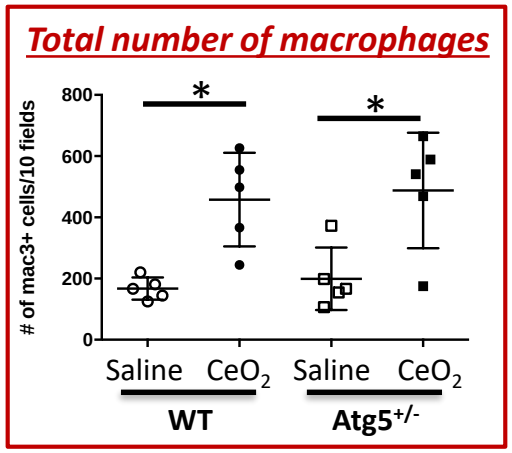


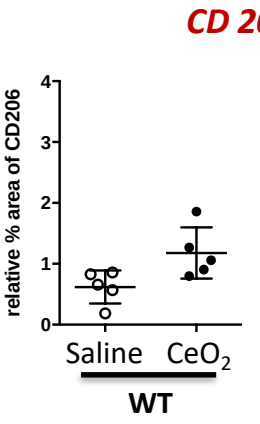


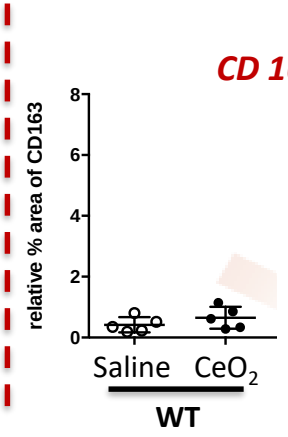


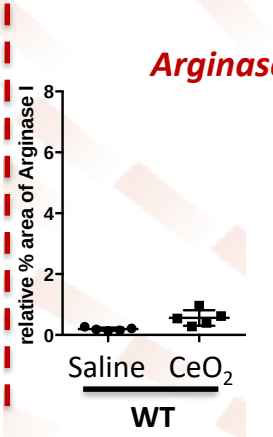
- **Deletion** of autophagy in **macrophages**

➔ **Modification of M1/M2 phenotype in favor of M2**

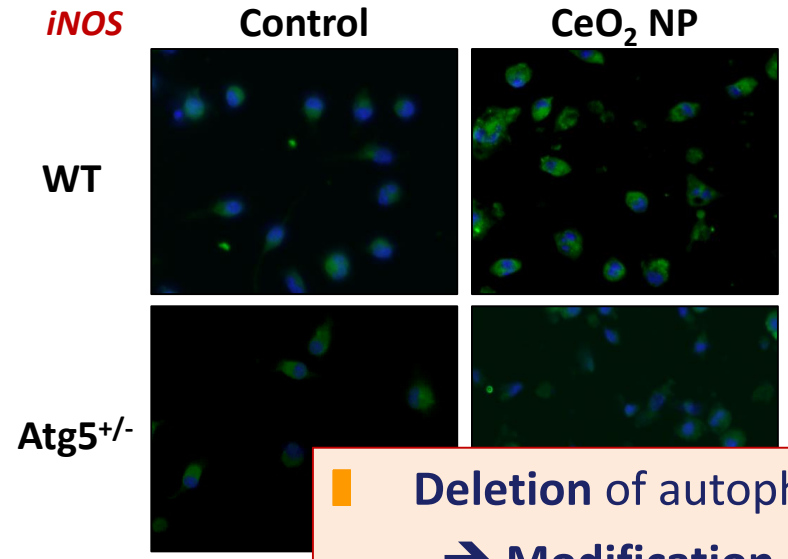


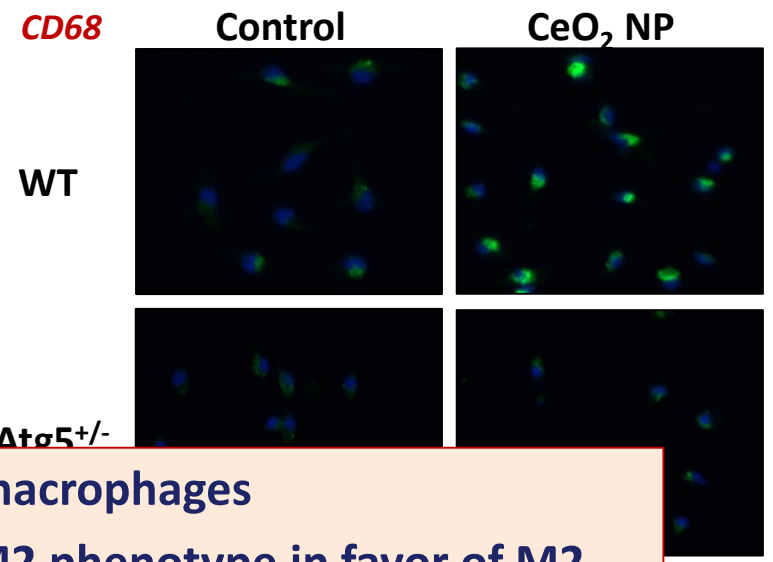




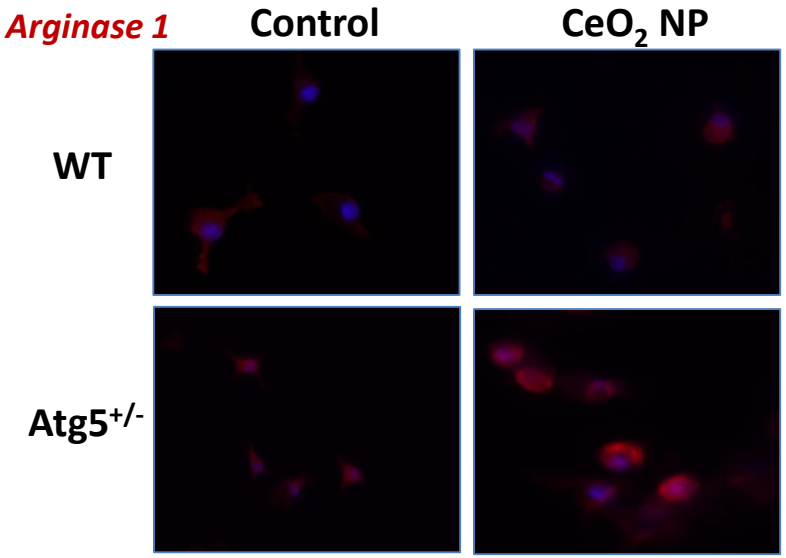


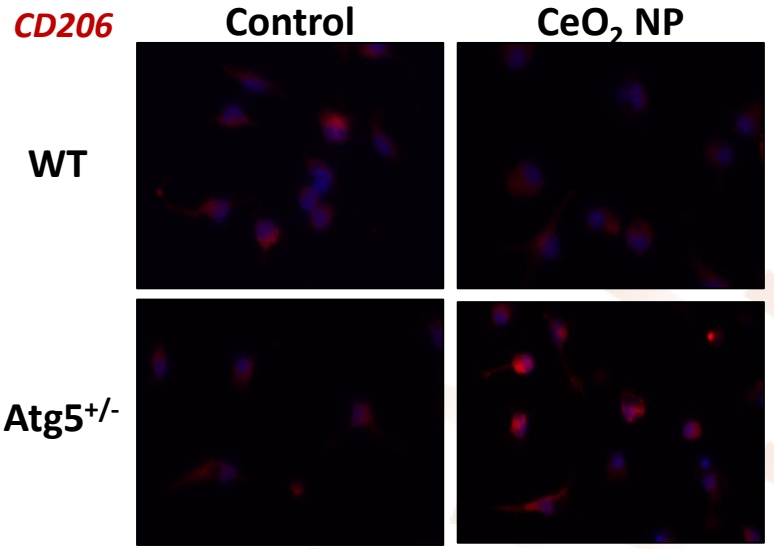
Mechanism of protection: modification of M1/M2 balance?





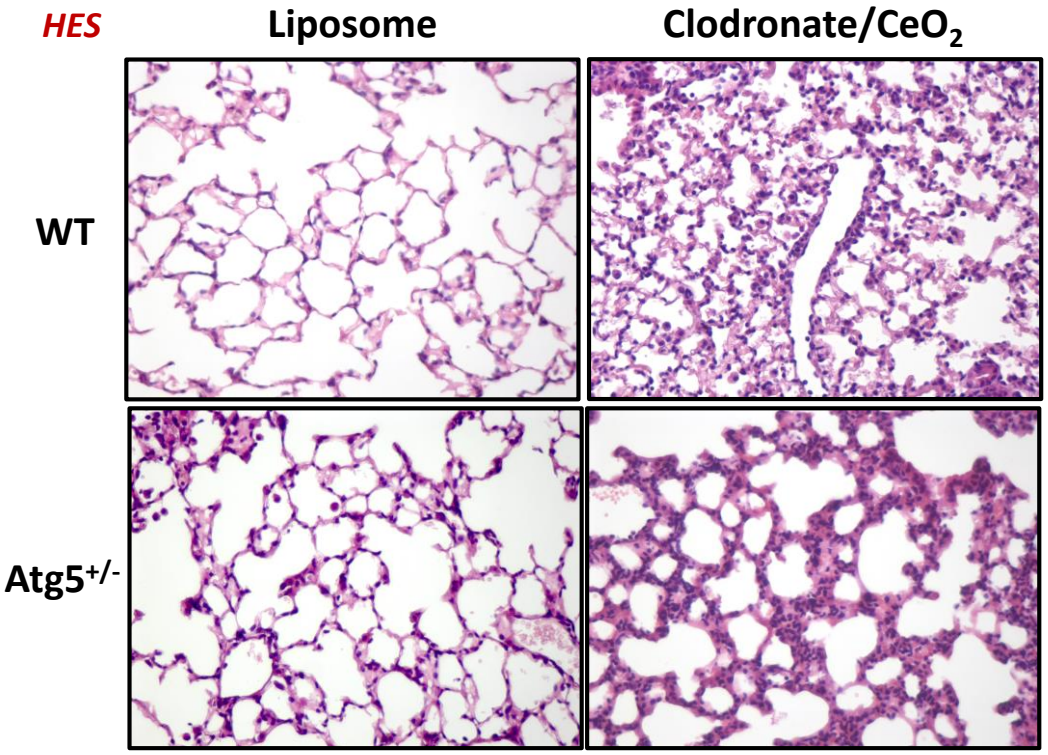
- **Deletion** of autophagy in **macrophages**
  - ➔ **Modification of M1/M2 phenotype in favor of M2**





Mechanism of protection: macrophage autophagy?

Oropharyngeal aspiration of saline of 50µg CeO_2 NP - Sacrifice 28 days later
Repeated administration of clodronate ➔ ***Depletion of macrophages***



- **Depletion of macrophages ➔ no more protection** against alveolar remodeling in Atg5+/- mice.

- **Exposure to CeO_2 NP** induces
  - **lung remodeling** in mice
  - **M1** macrophage **differenciation**
- **Deletion of macrophagic autophagy protects from alveolar remodeling and M1 differenciation**

➔ **Macrophagic autophagy: a new target to consider against lung remodeling?**

Thank you!

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