

# IMRB



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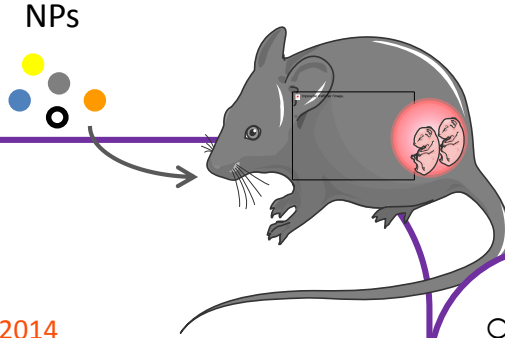


Exposure to manufactured nanoparticles during gestation: *impact on the respiratory tract of the offspring in a mouse model*

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# Pulmonary exposure to nanoparticles (NP)

## Consequences in adults



### ○ Lung remodelling:

- Granuloma (CNT and CeO<sub>2</sub>)

*Lam et al. 2004; Aalapati et al. 2014*

- Fibrosis (CNT, CeO<sub>2</sub>, TiO<sub>2</sub> and SiO<sub>2</sub>)

*Park et al. 2011; Ma et al. 2012; Morimoto et al. 2013; Ma et al. 2014*

- Emphysema (TiO<sub>2</sub>)

*Chen et al. 2006*

### ○ Underlying biological mechanism:

- Inflammation (TiO<sub>2</sub>, Ag and CeO<sub>2</sub>)

*Moon et al. 2010; Ma et al. 2011; Haberl et al. 2013; Mishra et al. 2016*

- Oxidative stress (TiO<sub>2</sub>, Ag, CeO<sub>2</sub> and SiO<sub>2</sub>)

*Park et al. 2008; Ha Ryong et al. 2011; Srinivas et al. 2011; Pen et al. 2014; Petrache Voicu et al. 2015*

- Genotoxicity (Ag and TiO<sub>2</sub>)

*Chen et al. 2006; Armand et al. 2016*

- Apoptosis (TiO<sub>2</sub>, CB and CeO<sub>2</sub>)

*Hussain et al. 2010, Rice et al. 2015*

## Consequences in the offspring

- **Reproduction alterations:** Decreased sperm production (TiO<sub>2</sub>, CB)

*Yoshida et al. 2010; Jackson et al. 2011; Hougaard et al. 2010*

- **Pregnancy complications:**

- Decreased pregnancy rate (Cd)
- Delayed fetal development (Cd)

*Blum et al. 2012*

- Decreased fetal weight (MWCNT)

*Fujitani et al. 2012*

- **Alteration of brain development** (CB, MWCNT and TiO<sub>2</sub>)

*Hougaard et al. 2010 & 2013; Jackson et al. 2011*

**Respiratory effects of maternal exposure during pregnancy?**

## Hypothesis

**Pulmonary exposure to NPs during pregnancy induces lung alterations in pups**

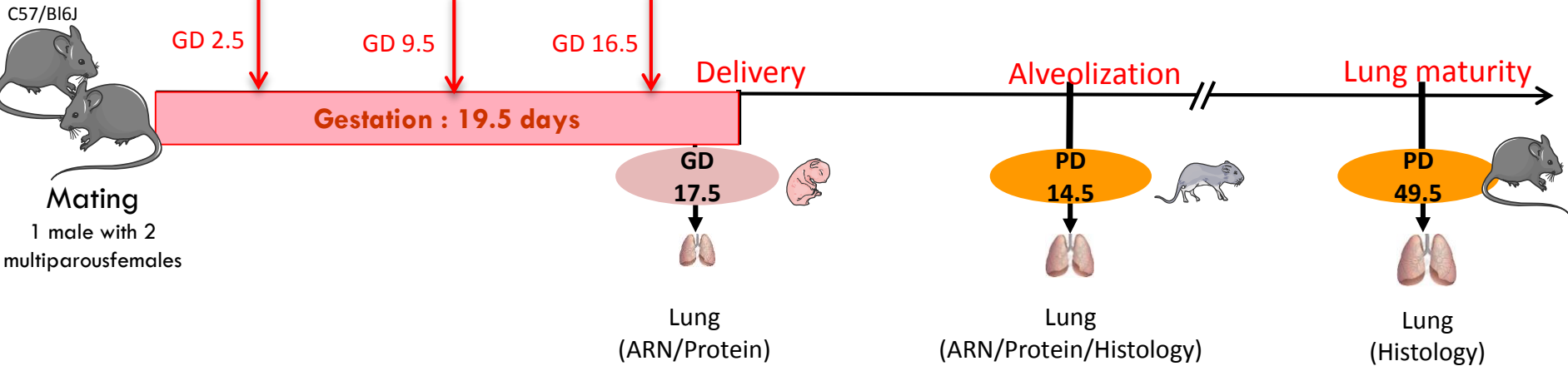
## Aims

- To assess the impact of exposure to 3 NPs during pregnancy on lung development
- To decipher the underlying mechanisms involved in lung alterations (direct or indirect?)

# Methodology

## Experimental protocol

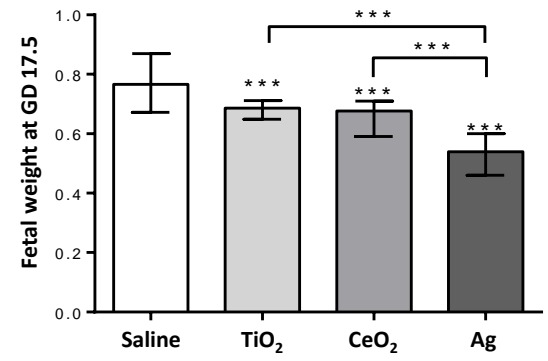
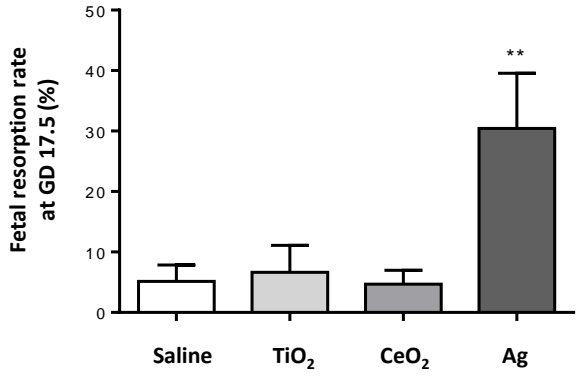
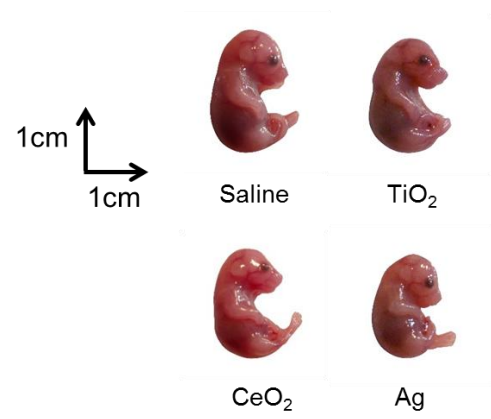
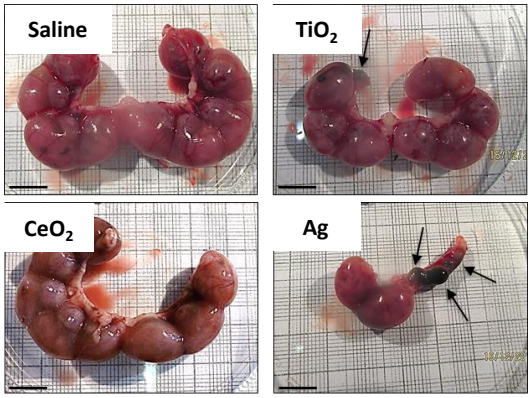
**Non-surgical intratracheal instillation** of pregnant mice  
(once a week)  
Saline or NPs (100µg): **TiO<sub>2</sub>** (insoluble), **CeO<sub>2</sub>** (insoluble)  
or **Ag** (soluble), all spherical, diameter: 10-20 nm



GD : Gestational day  
PD : Post delivery day

# Results: Fetotoxicity

- Effect of NPs on fetuses at GD 17.5:

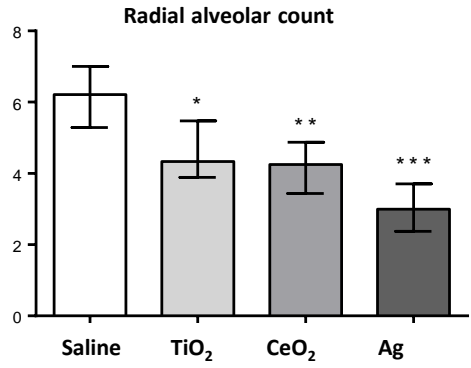
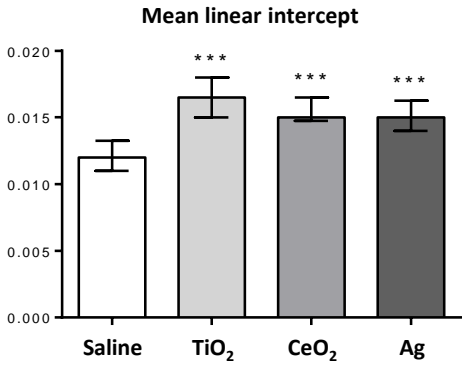
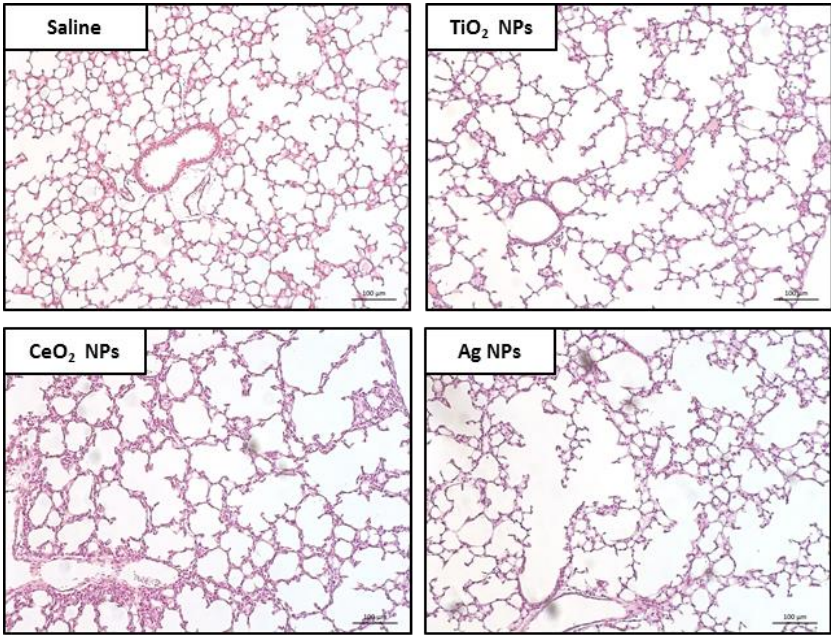


Significant increase of fetal death after AgNPs treatment

Significant decrease of fetal weight after maternal exposure to NPs

# Results: impairment of lung development

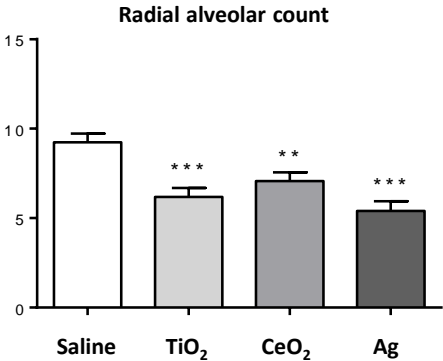
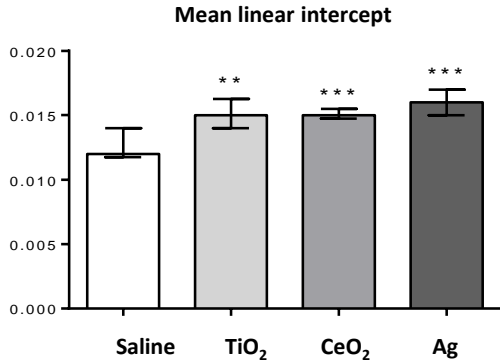
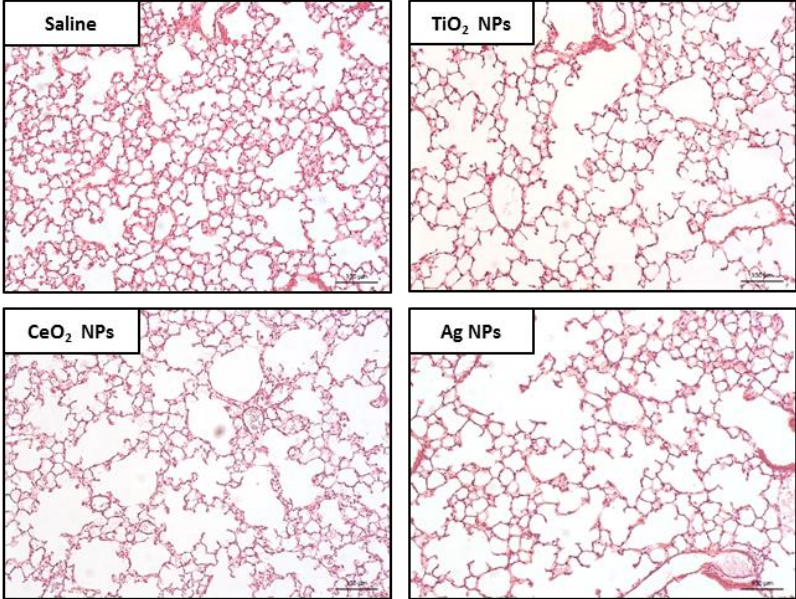
- Effect of NPs on lung development at PD 14.5:



Significant **decrease in the alveolization** of the offspring at PD 14.5 whatever the NPs treatment

# Results: impairment of lung development

- Effect of NPs in lung development at PD 49.5:



Significant decrease in the alveolization of the offspring at PD 49.5 whatever the NPs treatment



Pulmonary exposure to NP during pregnancy induces an impairment of lung development with a persistent effect at adult age

# Which possible mechanisms ?



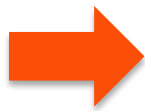


# Results: ① Inflammatory response

- Cytokines and chemokines in the amniotic fluid (*Luminex*<sup>®</sup>) and fetal lung (*qPCR*, *Luminex*<sup>®</sup>):

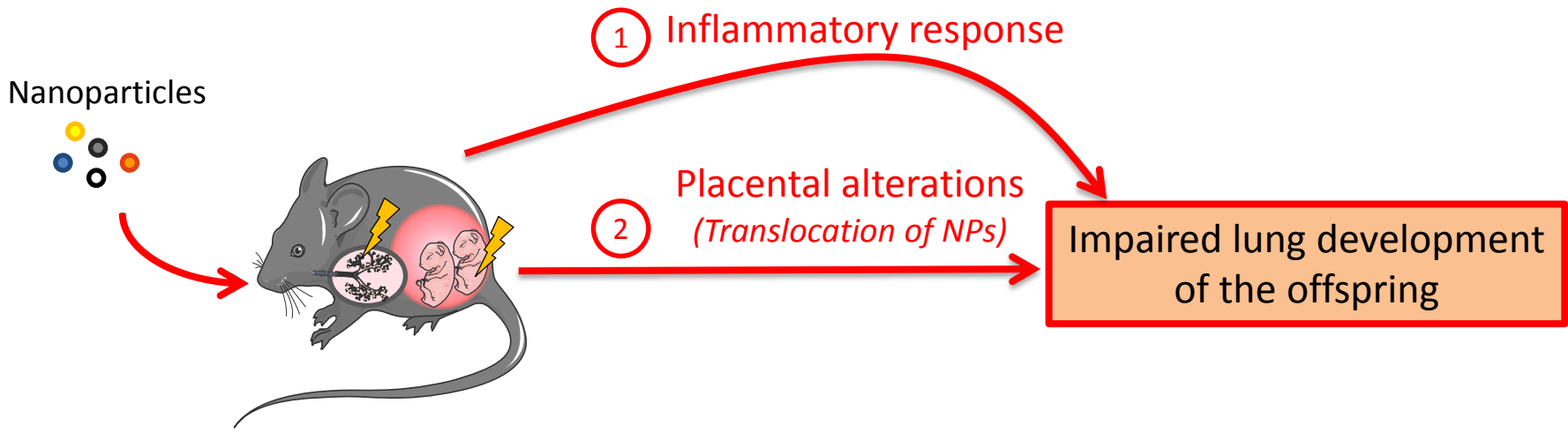
G-CSF, GM-CSF, IL-1 $\beta$ , IL-2, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17, IP-10, KC, MCP-1, MIP-1 $\alpha$ , MIP-1 $\beta$ , MIP-2, TNF- $\alpha$  and VEGF

No inflammation in the amniotic fluid or the fetal lung



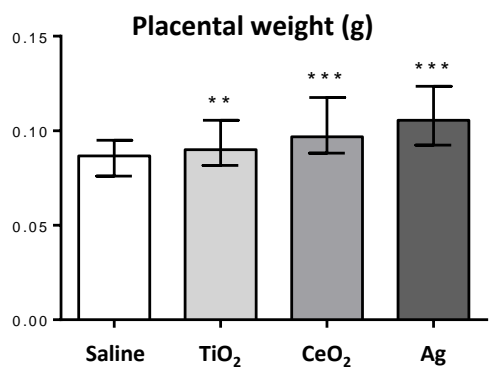
**Inflammation might not be the mechanism involved in the lung impairment of the offspring**

# Which possible mechanisms ?

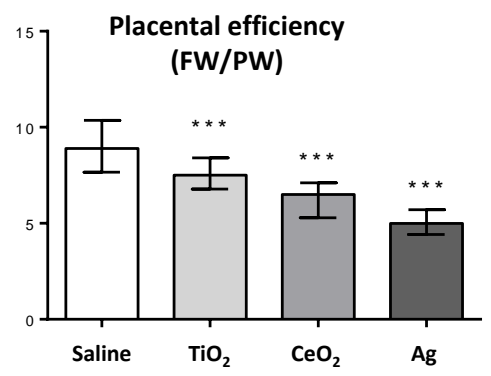


# Results: ② Placental alteration

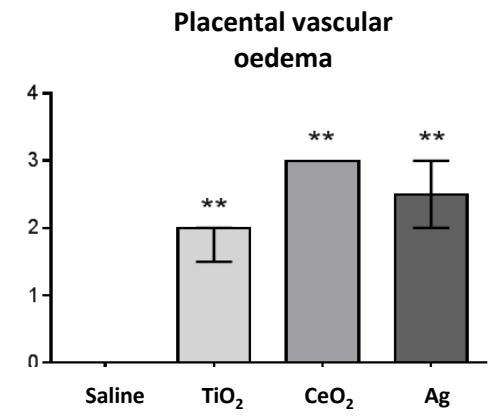
- Placental alteration at GD 17.5:



NP exposure increases placental weight



NP exposure decreases placental efficiency



NP exposure induces placental vascular oedema



**NP exposure during pregnancy induces placental alterations**

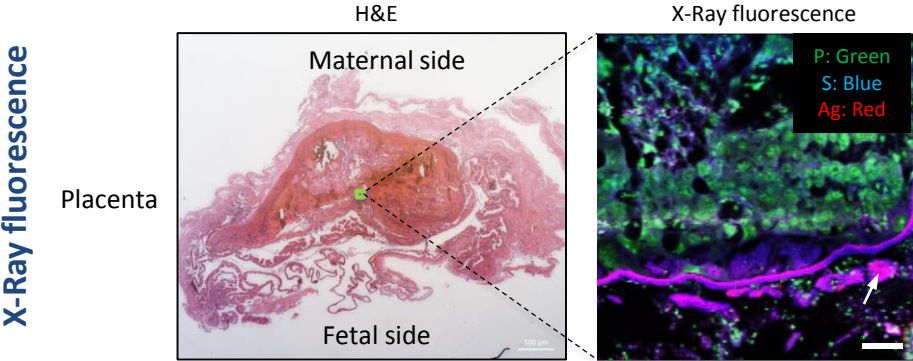
Direct toxic effect of NPs?

# Results: 2 Placental alteration

- NPs translocation into the placenta:

		Element concentration in µg/g (median with interquartile ranges)		
		Ti	Ce	Ag
ICP-MS assay Placenta	Saline	0.611 (0.256-1.431)	0.001 (0.001-0.001)	0.001 (0.001-0.003)
	TiO <sub>2</sub>	5.092 (1.624-5.513)***		
	CeO <sub>2</sub>		0.004 (0.001-0.007)**	
	Ag			5.484 (2.872-7.136)***

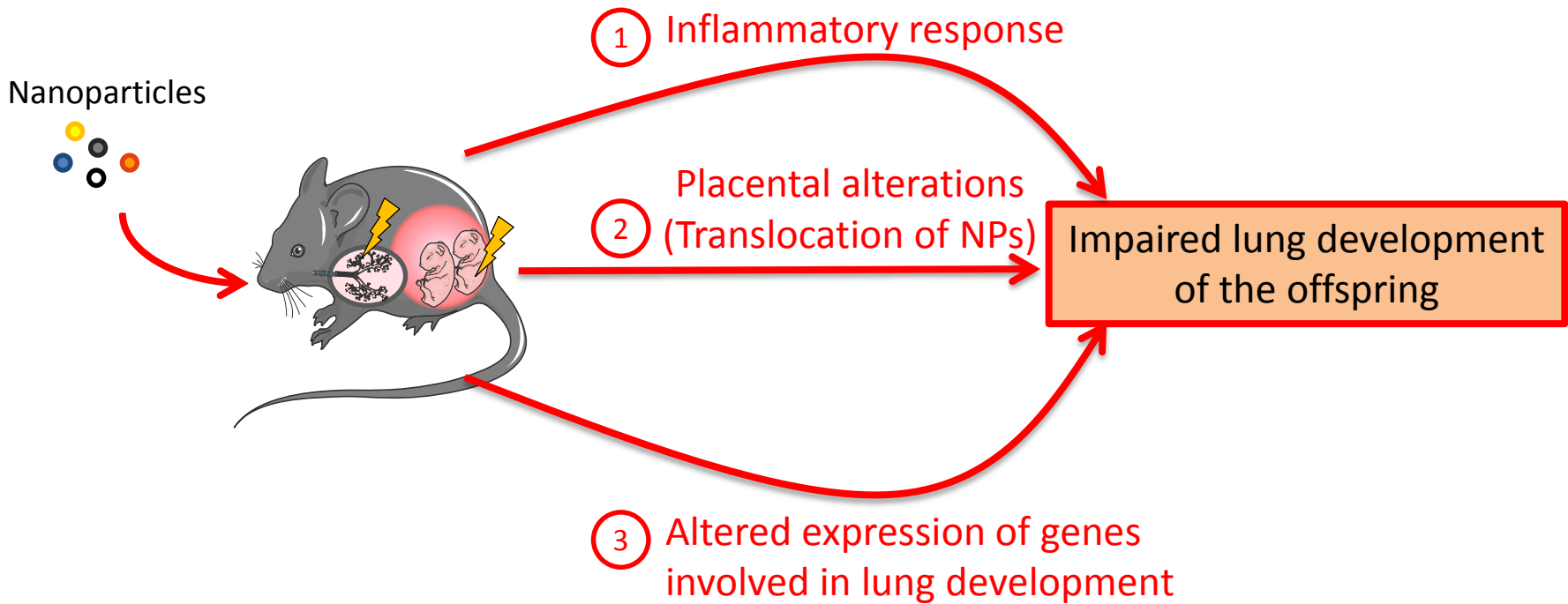
Ti, Ce and Ag elements are found in the placenta



Ag is detected in the chorionic plate of the placenta, mostly in the nano form (measured by XANES)

➔ **NPs are found in the placenta and may be involved in the placental alterations**

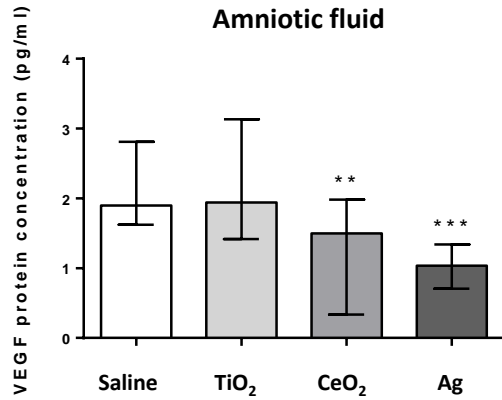
# Which possible mechanisms ?



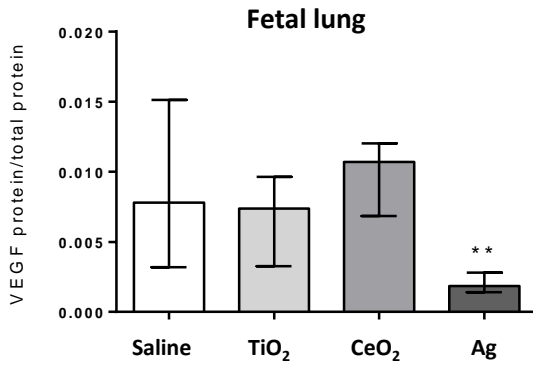
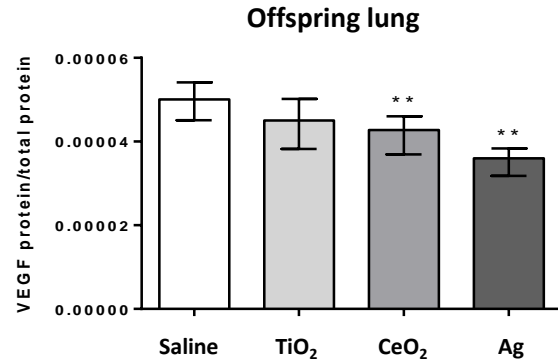
# Results: 3 Effect of NPs on VEGF expression ?

- VEGF expression:

Gestational Day 17.5



Post-delivery Day 14.5



VEGF expression decreases significantly at different stages of lung development

# Conclusion

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- **Pulmonary exposure to NPs during pregnancy induces:**
  - Fetotoxicity (fetal death, decreasing weight of fetuses)
  - Lung impairment with decreased alveolization, with a persistent effect at adult age
  
- **At least 2 mechanisms could be involved in lung impairment:**
  - Placental alterations (efficiency, oedema → link with presence of NP?)
  - Downregulation of the expression of VEGF (FGF-18, MMP-9?)

THANK YOU



**IMRB Team Lanone/Boczkowski**  
*Respiratory effects of environmental contaminants*



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Erwan Paineau



Delphine Vantelon



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