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The Neutralization of CD40/CD40L Complex Inhibits TRALI Development in a Mouse Model Induced through Lipopolysaccharide and Anti-MHC I mAb Injections

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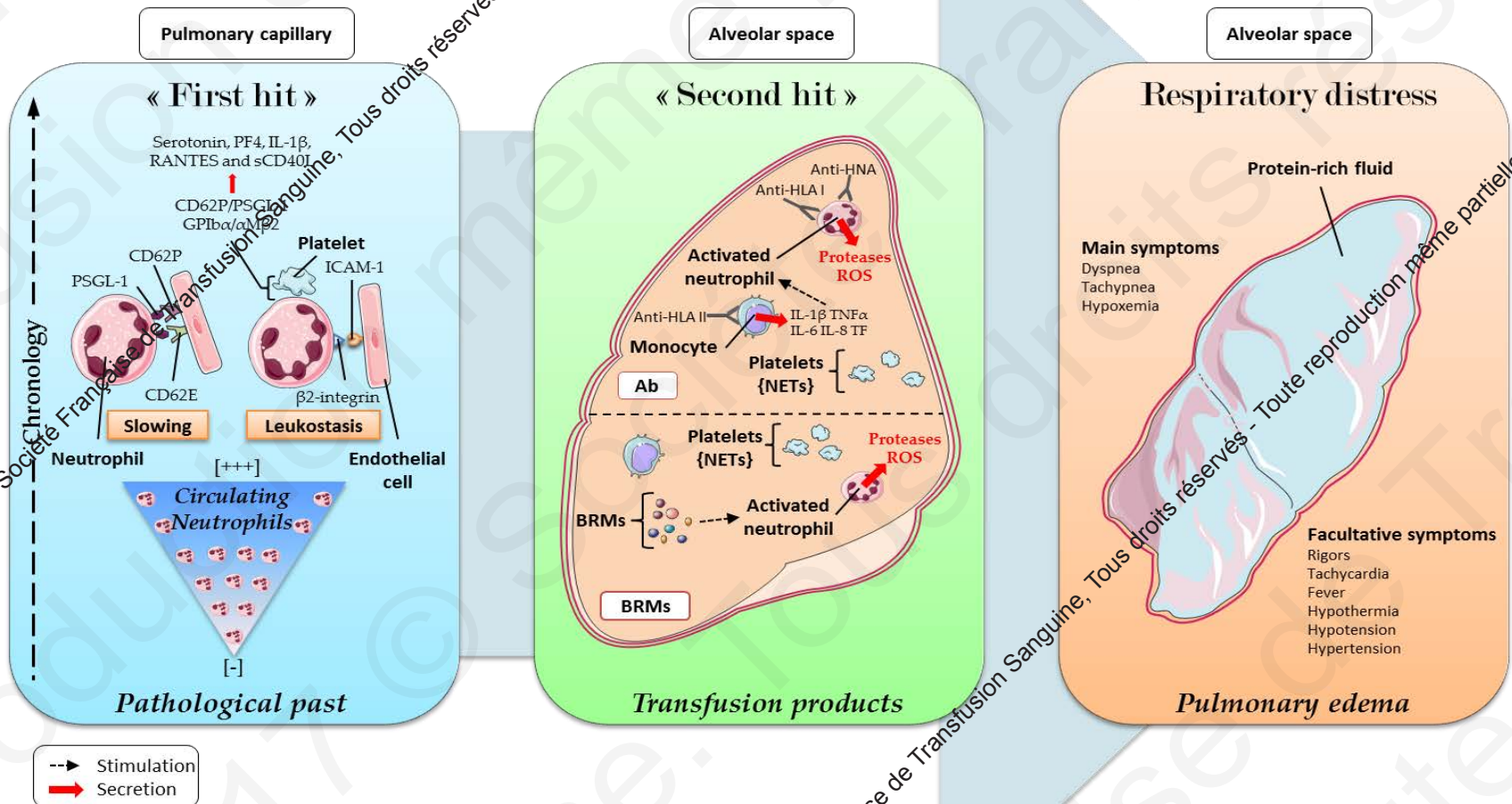
INTRODUCTION - Methods - Results - Conclusion

- ❖ **ALI:** medical condition occurring in critically ill patients characterized by inflammation in the lungs
- ❖ **TRALI:** Acute respiratory distress after blood transfusion
 - ❑ Occurs within the 6 hours after blood transfusion,
 - ❑ High rate of mortality,
 - ❑ A frequency at 0.08% in transfused patient,
 - ❑ Manifestations: Dyspnea, Tachypnea and Hypoxia.
- ❖ **Products:**
 - ❑ Anti-HLA I & II; Anti-HNA,
 - ❑ Biological response modifiers (BRMs).



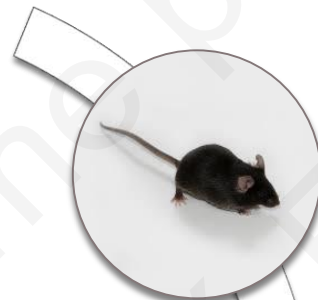
From Vlaar et al. 2013. Lancet

INTRODUCTION - Methods - Results - Conclusion



INTRODUCTION - Methods - Results - Conclusion

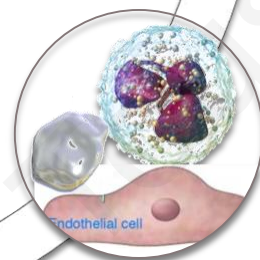
**CD40/
CD40L
(sCD40L*)**



Implicated in mouse ALI development ²



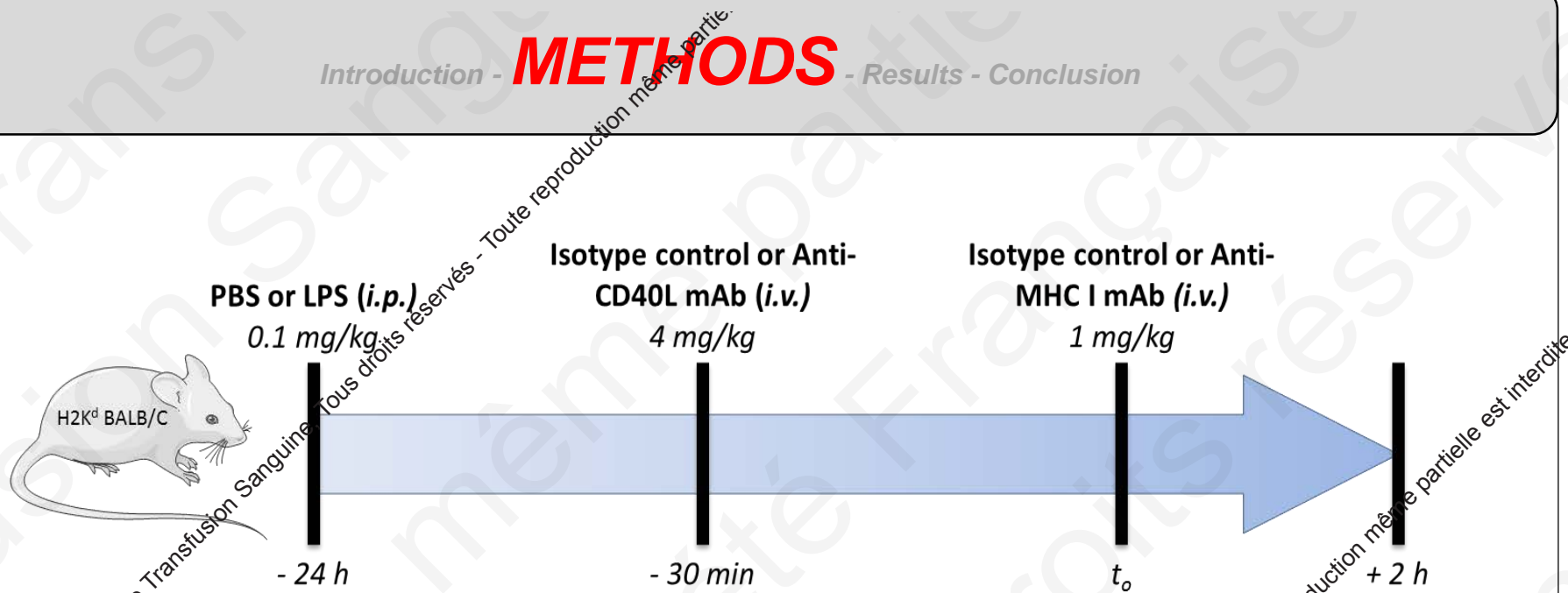
High sCD40L detected in PC implicated in TRALI ³



Platelet/Neutrophil/EC Interaction ^{4,5,6}

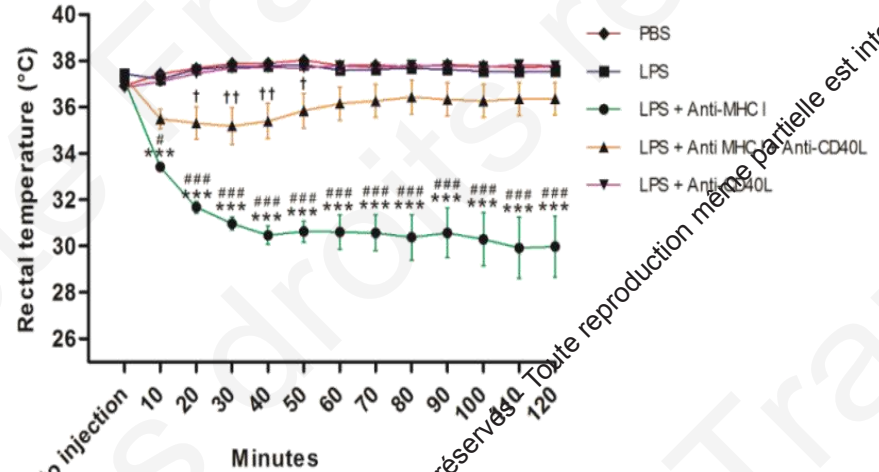
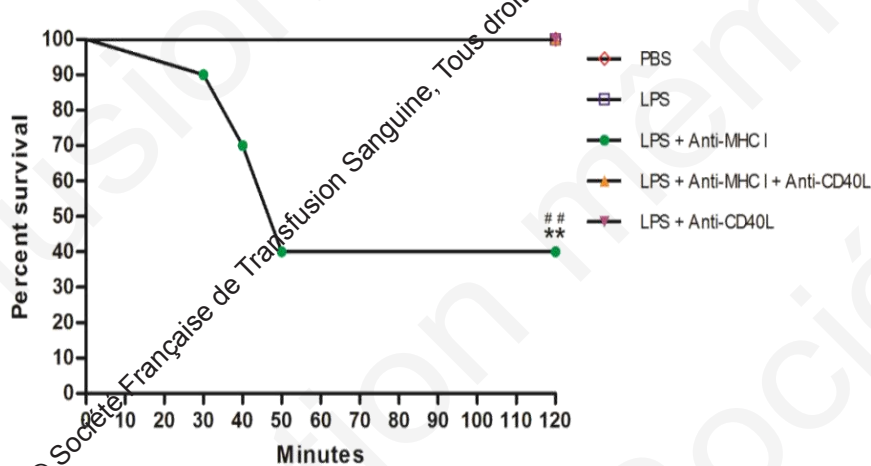
* 95% of sCD40L is released from platelets ¹

- 1 Andre P *et al.* 2002. *Circulation*
- 2 Adawi A *et al.* 1998. *Am J Pathol*
- 3 Kaufman J *et al.* 2007. *J Thromb Haemost*
- 4 Vanichakarn P. 2008. *Thromb Res*
- 5 Henn V. 1998. *Nature*
- 6 Kotowicz K. 2000. *Immunology*



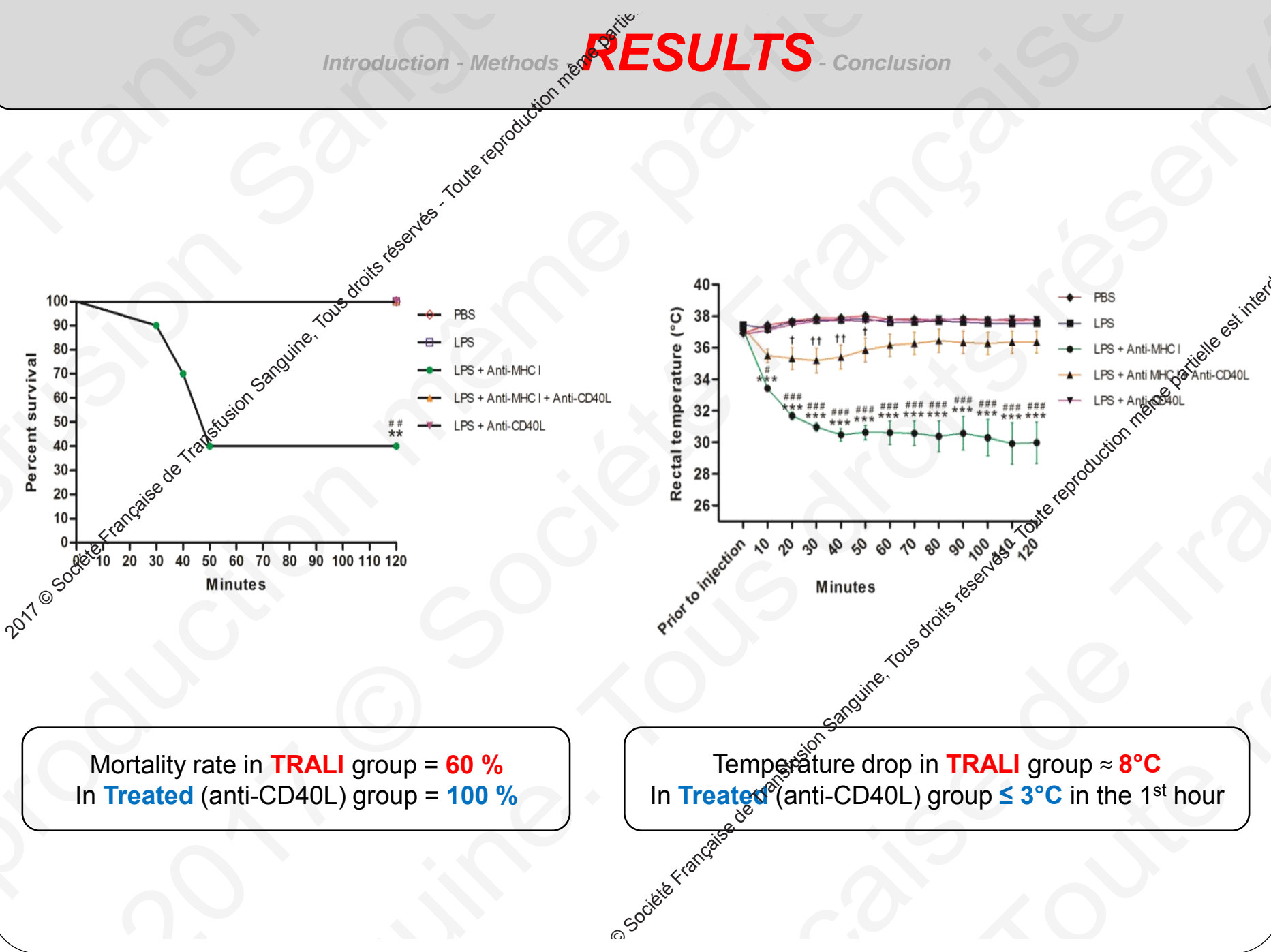
PBS	PBS Injection (<i>i.p.</i>)	Isotype Control Injection (<i>i.v.</i>)	Isotype Control Injection (<i>i.v.</i>)
LPS	LPS Injection (<i>i.p.</i>)	Isotype Control Injection (<i>i.v.</i>)	Isotype Control Injection (<i>i.v.</i>)
LPS + Anti-MHC I	LPS Injection (<i>i.p.</i>)	Isotype Control Injection (<i>i.v.</i>)	Anti-MHC I Injection (<i>i.v.</i>)
LPS + Anti-MHC I + Anti-CD40L	LPS Injection (<i>i.p.</i>)	Anti-CD40L Injection (<i>i.v.</i>)	Anti-MHC I Injection (<i>i.v.</i>)
LPS + Anti-CD40L	LPS Injection (<i>i.p.</i>)	Anti-CD40L Injection (<i>i.v.</i>)	Isotype Control Injection (<i>i.v.</i>)

RESULTS



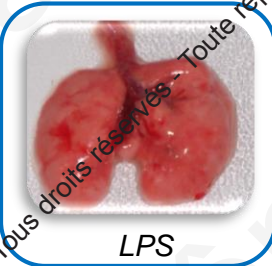
Mortality rate in **TRALI** group = **60 %**
 In **Treated** (anti-CD40L) group = **100 %**

Temperature drop in **TRALI** group \approx **8°C**
 In **Treated** (anti-CD40L) group \leq **3°C** in the 1st hour

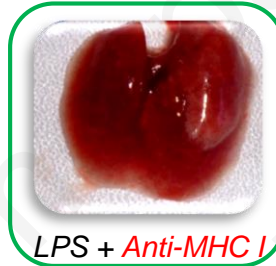




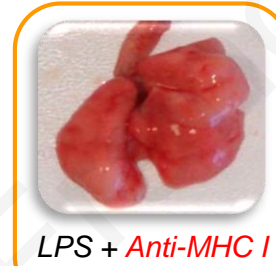
PBS



LPS



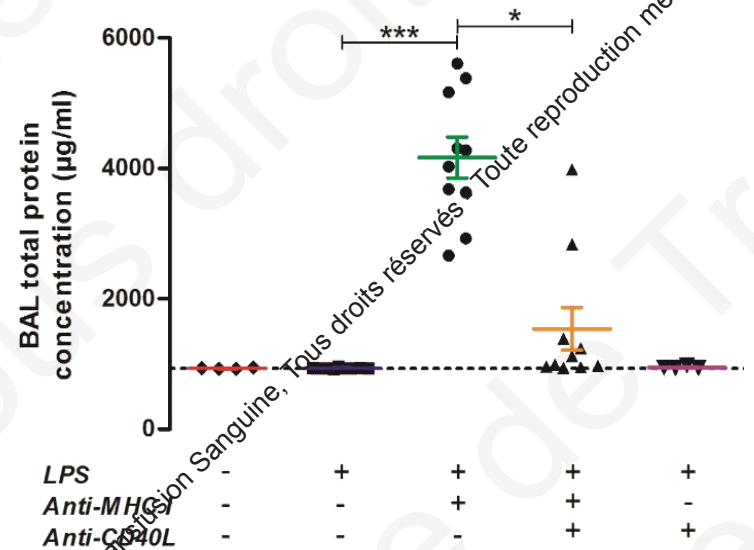
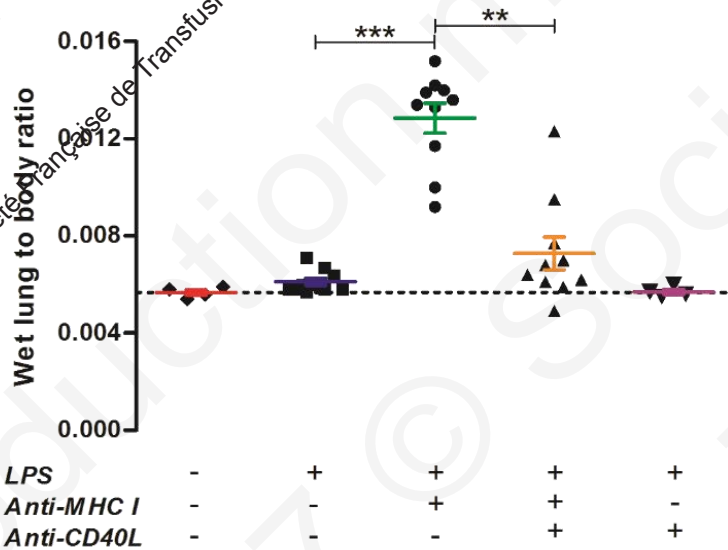
LPS + *Anti-MHC I*



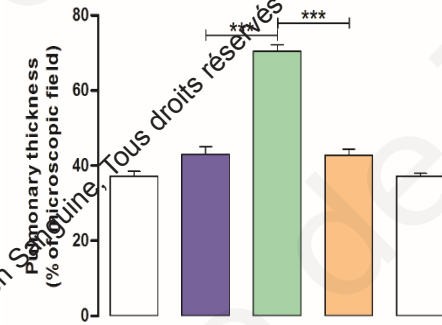
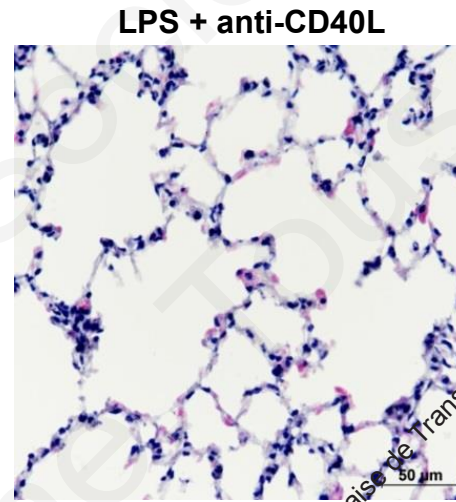
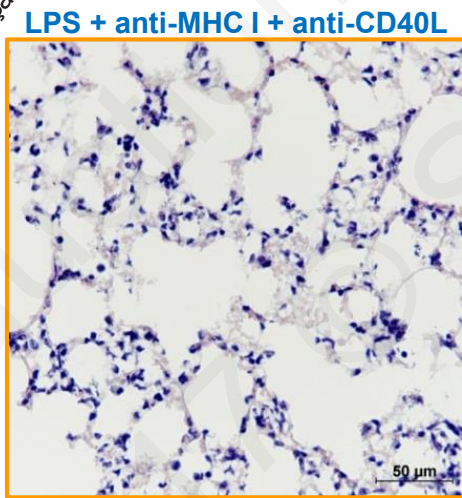
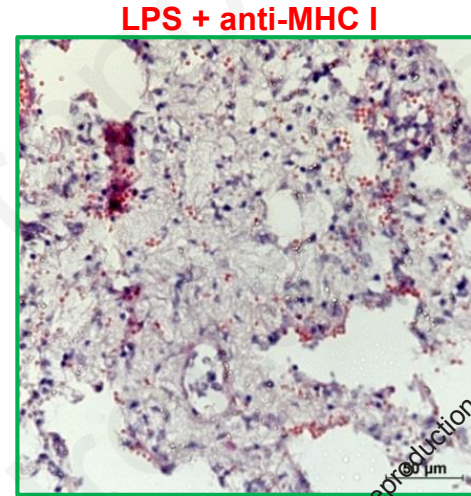
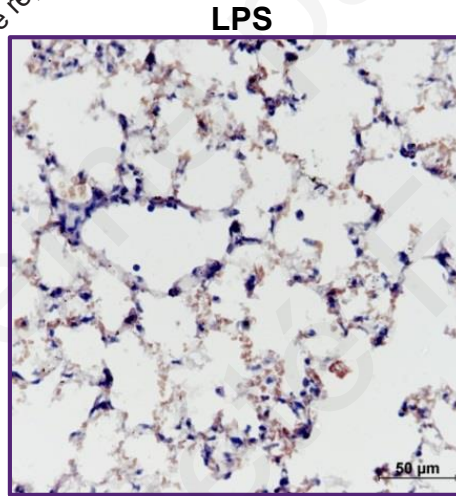
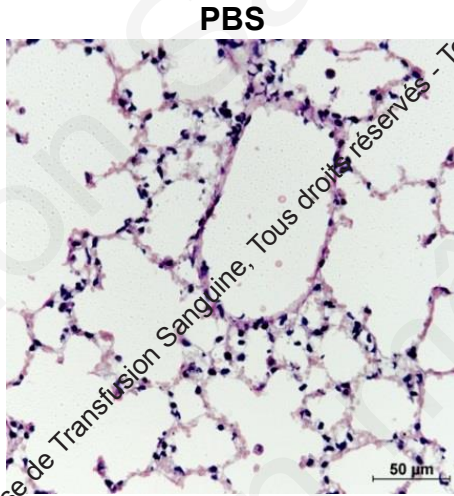
LPS + *Anti-MHC I*
+ *Anti-CD40L*



LPS + *Anti-CD40L*



Pulmonary edema development **is inhibited** through **anti-CD40L** mAb injection



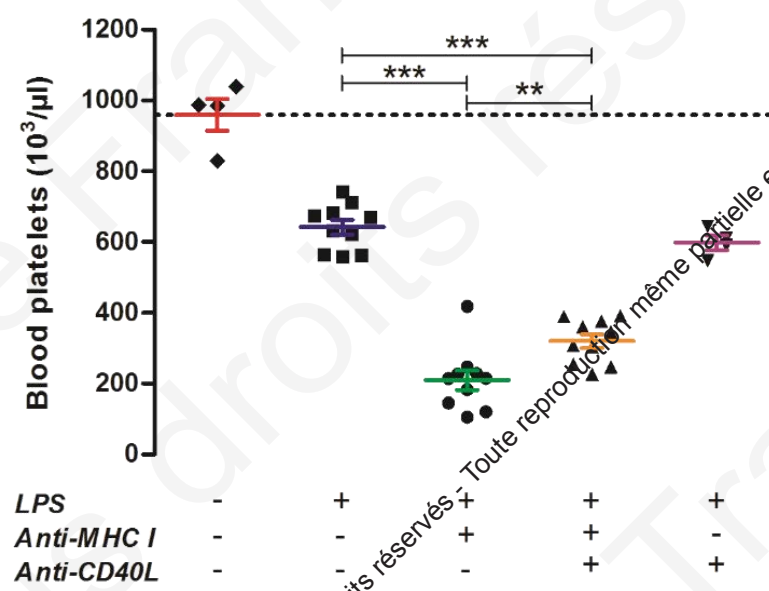
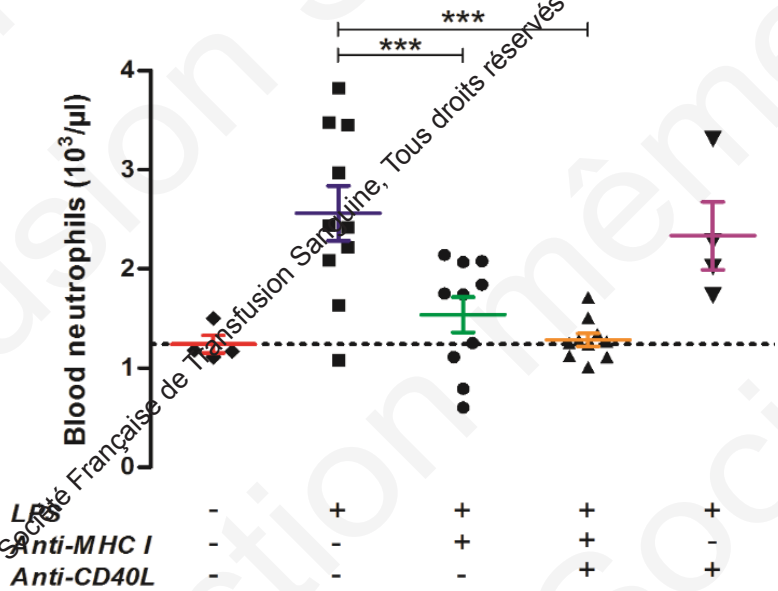
LPS	-	+	+	+	+
Anti-MHC I	-	-	+	+	-
Anti-CD40L	-	-	-	+	+

Pulmonary infiltration is inhibited through **anti-CD40L** mAb injection

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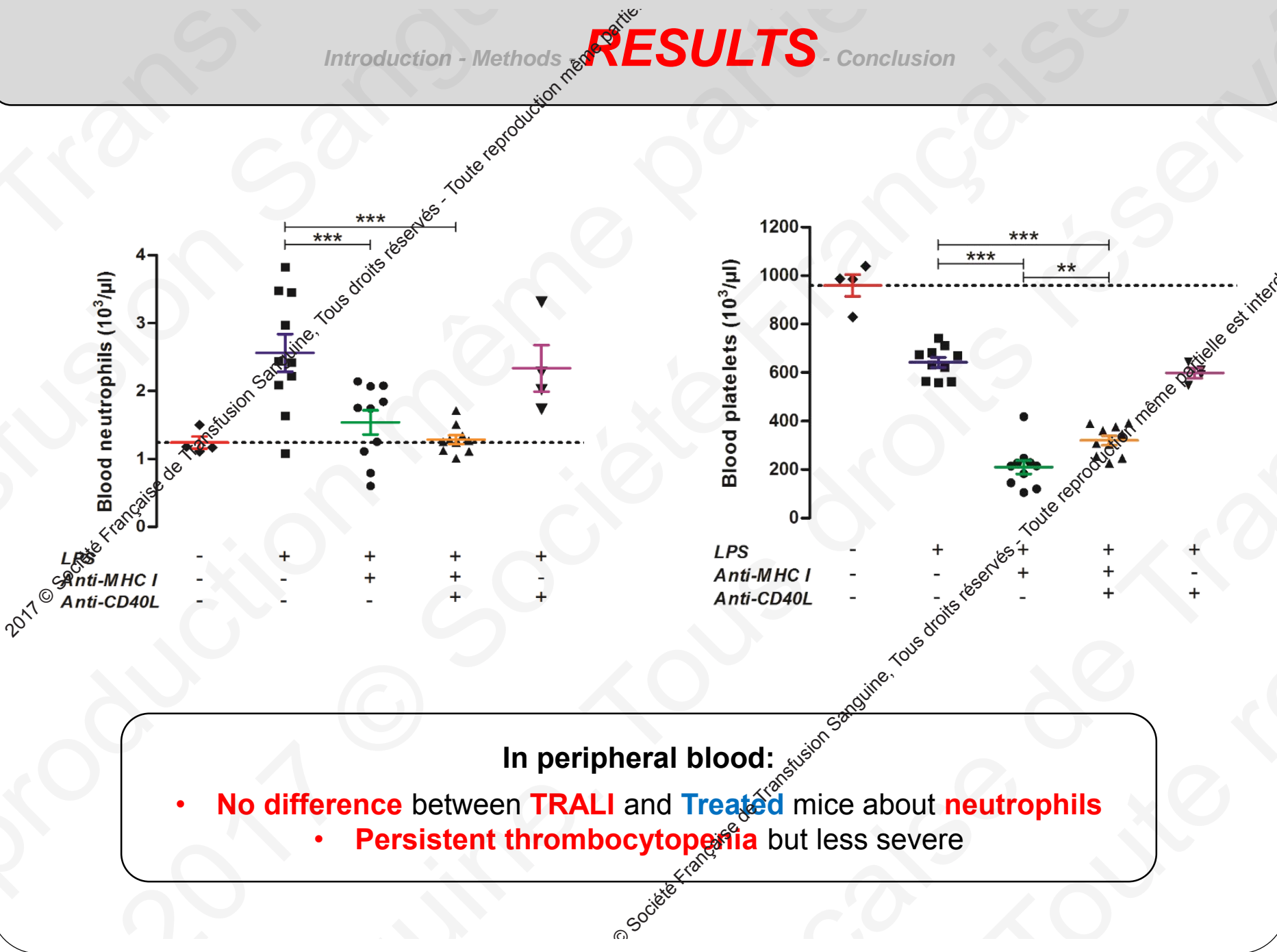
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RESULTS



In peripheral blood:

- **No difference** between **TRALI** and **Treated** mice about **neutrophils**
- **Persistent thrombocytopenia** but less severe



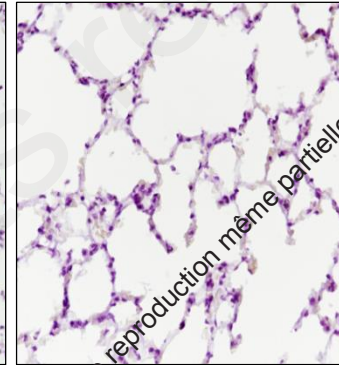
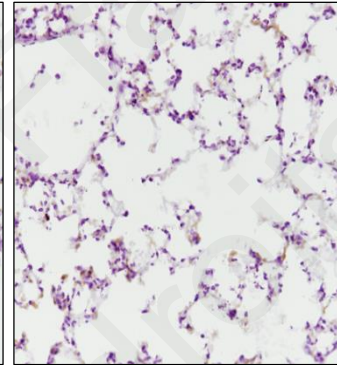
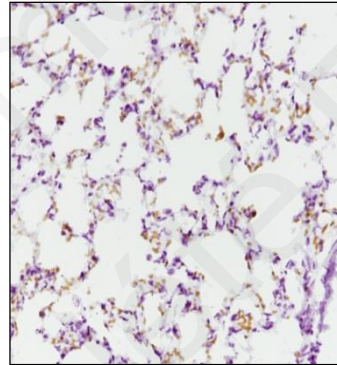
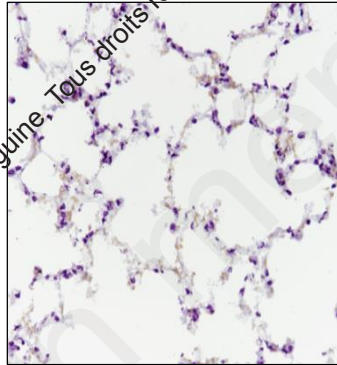
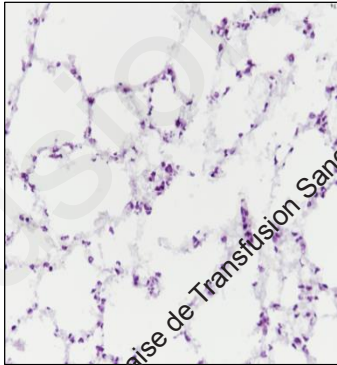
PBS

LPS

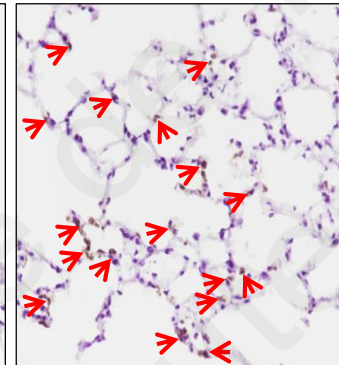
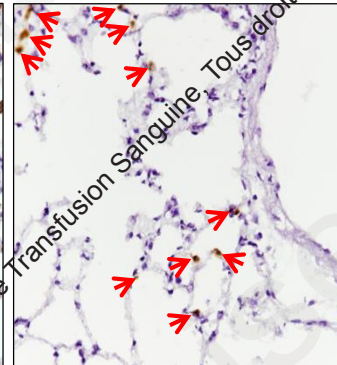
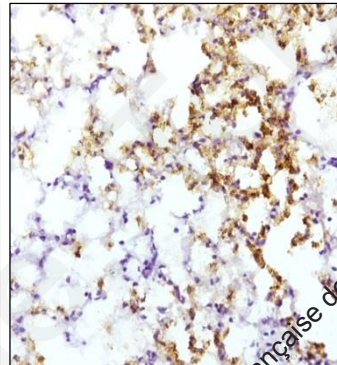
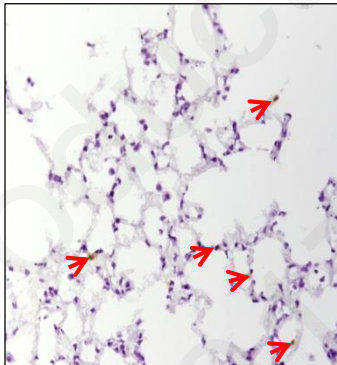
**LPS +
Anti-MHC I**

**LPS +
Anti-MHC I +
Anti-CD40L**

**LPS +
Anti-CD40L**

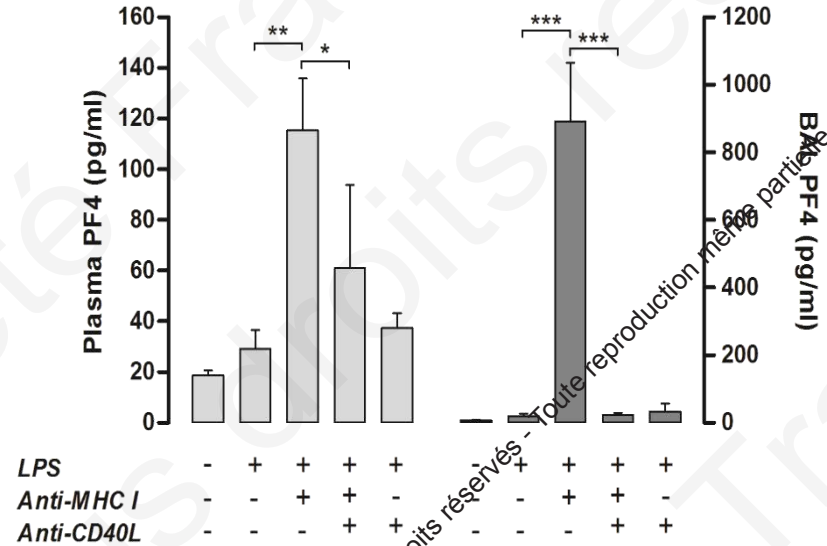
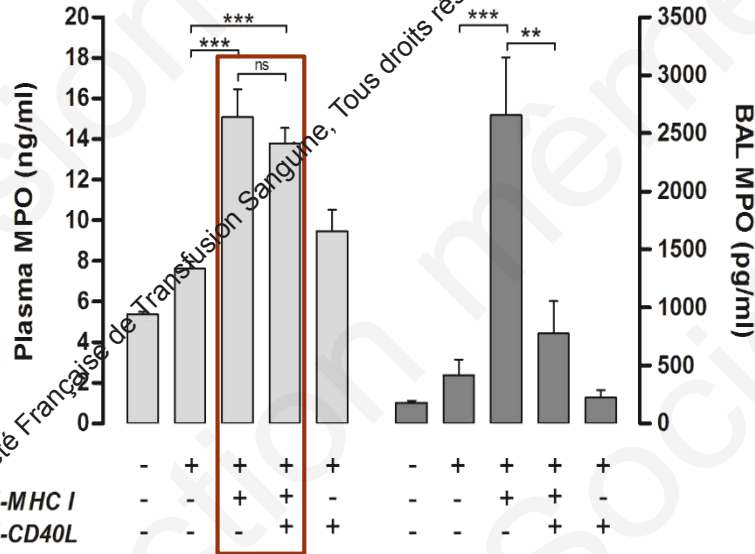


1st Line : Platelets Anti-CD41



2nd Line : Neutrophils Anti-Ly6G

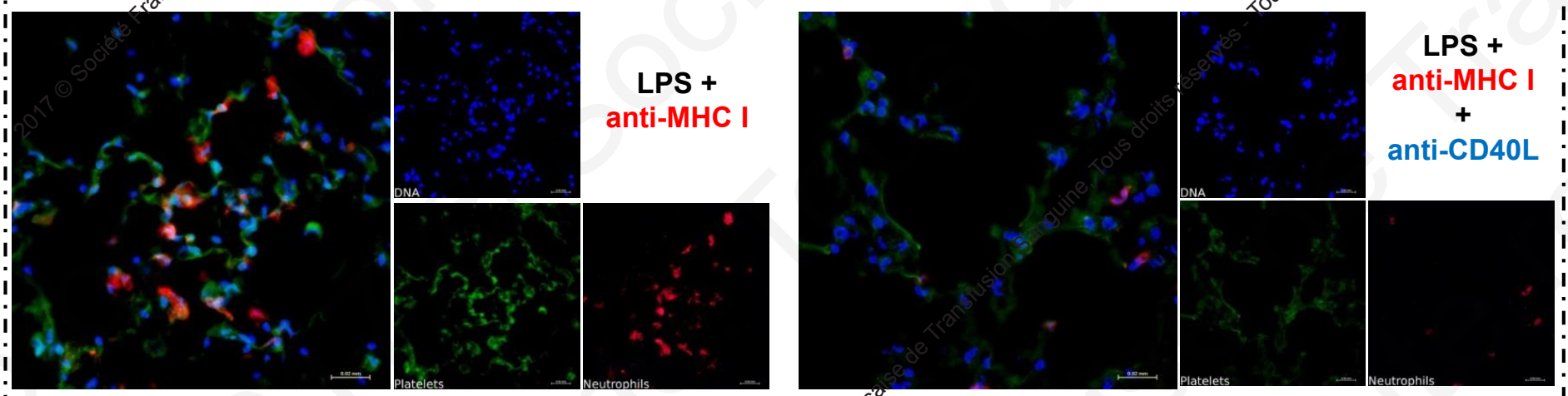
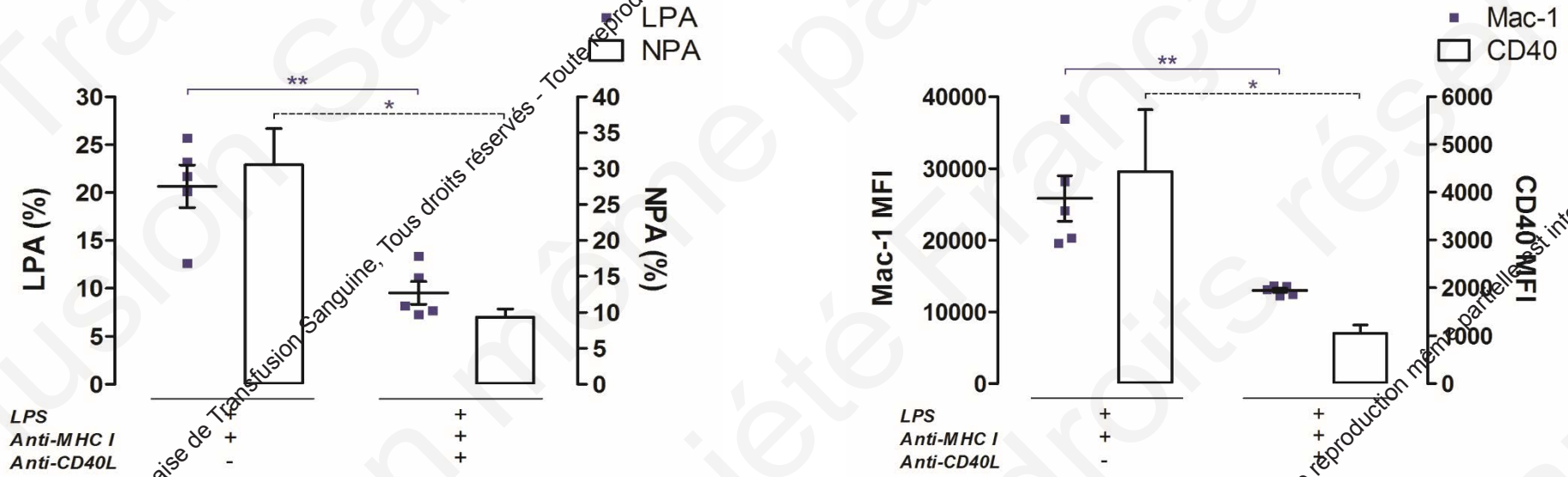
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Anti-CD40L injection decreases platelet activation
 but **not blood neutrophil activation**

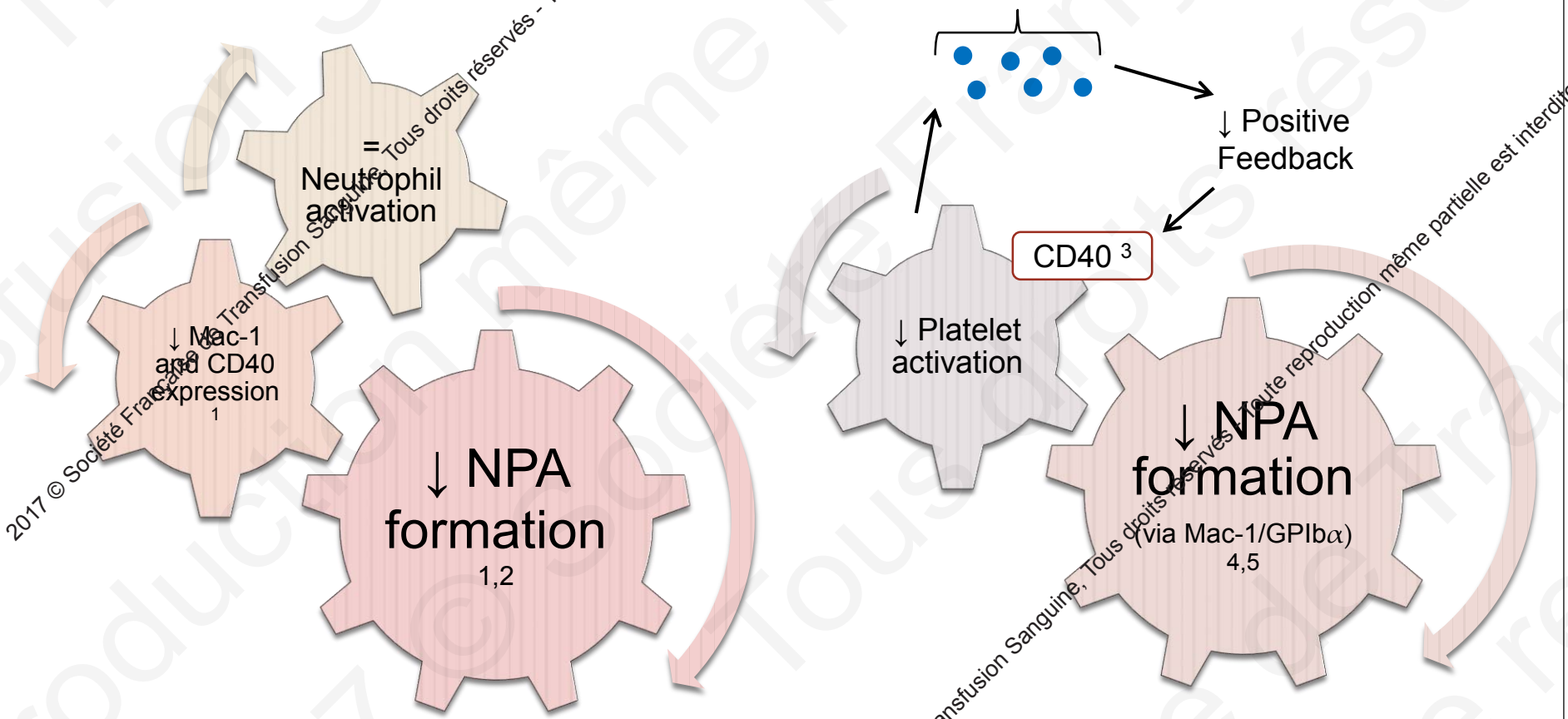
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Anti-CD40L injection decreases significantly neutrophil-platelet interaction

CD40/CD40L (sCD40L) inhibition:



↓ **PMN Migration = TRALI**

1. Jin R et al. 2013. PLoS One
2. Zuchtriegel G et al. 2016. PLoS bio
3. Andre P et al. 2002. Circulation
4. Caudrillier A et al. 2012. Curr Pharm Des
5. Zago AC et al. 2008. Arg Bras Cardiol

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FINANCIAL SUPPORT



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