Role of co-inhibitory pathways during experimental infection by *Trypanosoma cruzi* Tulahuen strain.

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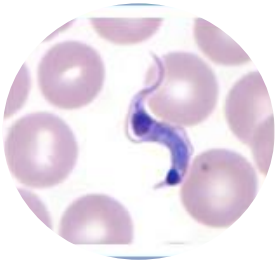
Chagas disease – Human American trypanosomiasis



- Chronic infection induced by the protozoan ***Trypanosoma cruzi***

- 20 million people infected (Mexico, Central and South America) and 100 million (25% LA population) at risk.
- Global incidence: 56,000 new cases/year and 12,000 deaths/year

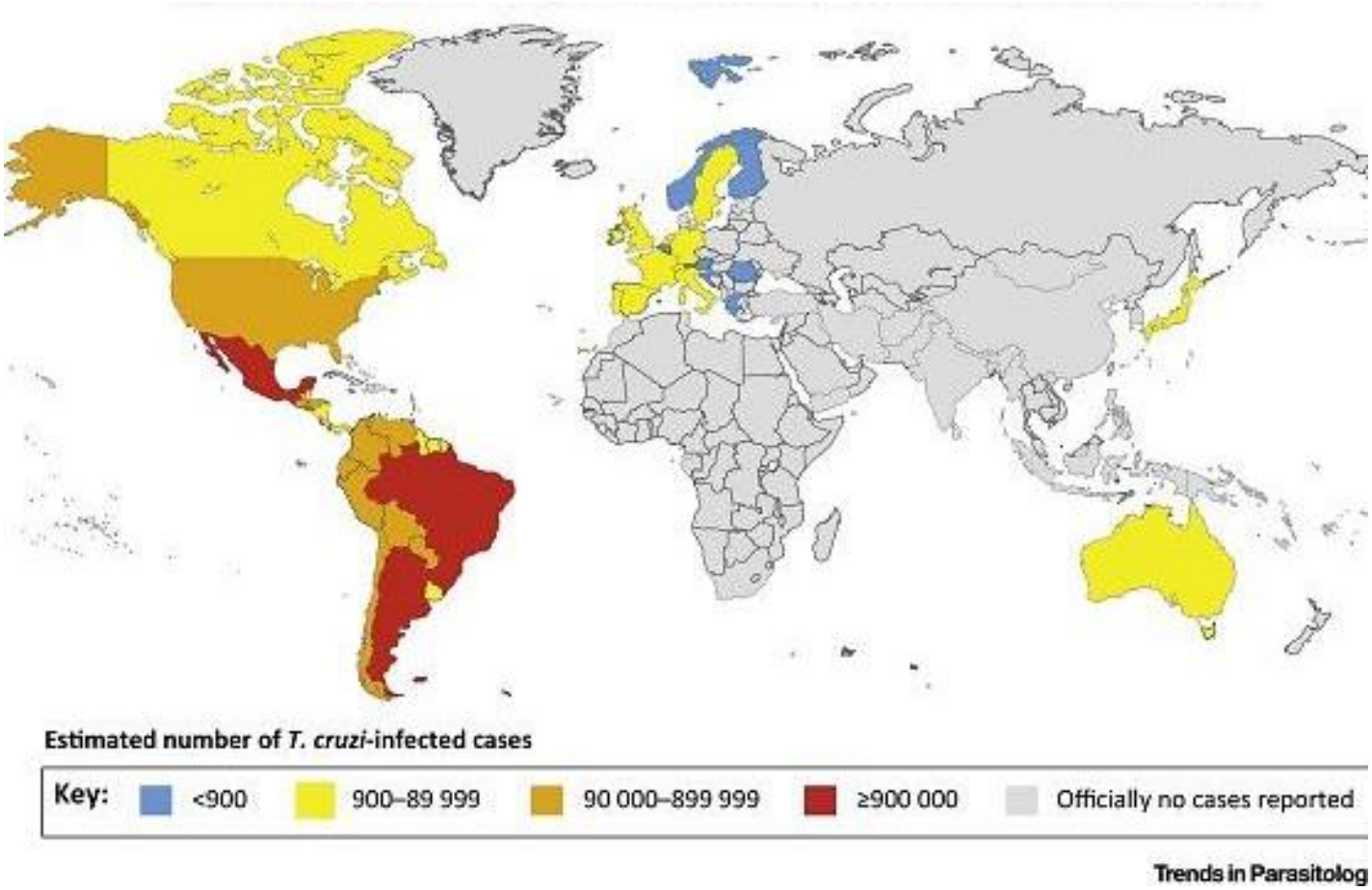
- Main mechanism of transmission:
  Vector: haematophagous insect,
  Subfamily: Triatominae

- Others: Congenital,
  blood transfusion,
  organ transplantation,
  accidental laboratory exposure and
  oral (food and drinks contaminated)

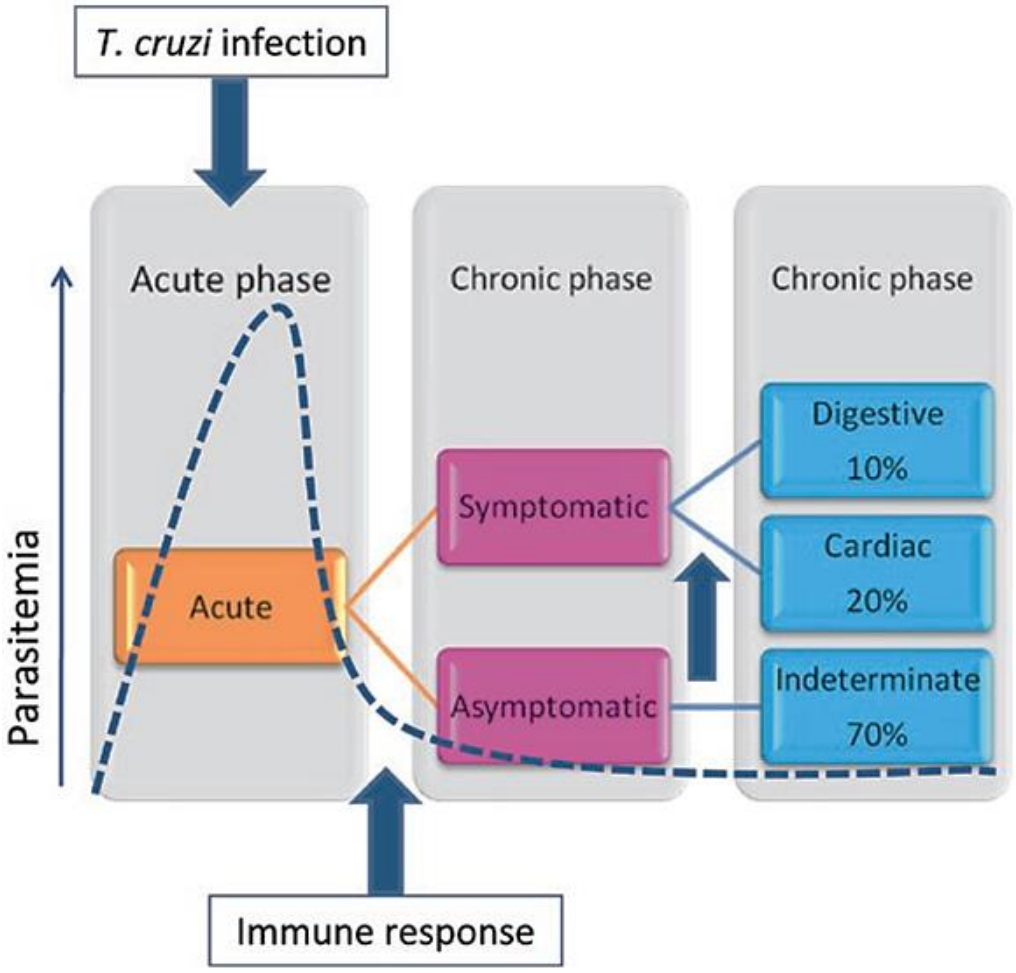
- Drugs: Benznidazole – Nefurtimox

- Vaccines are not available.

Global distribution of cases of chagas disease, based on official estimates, 2006-2010

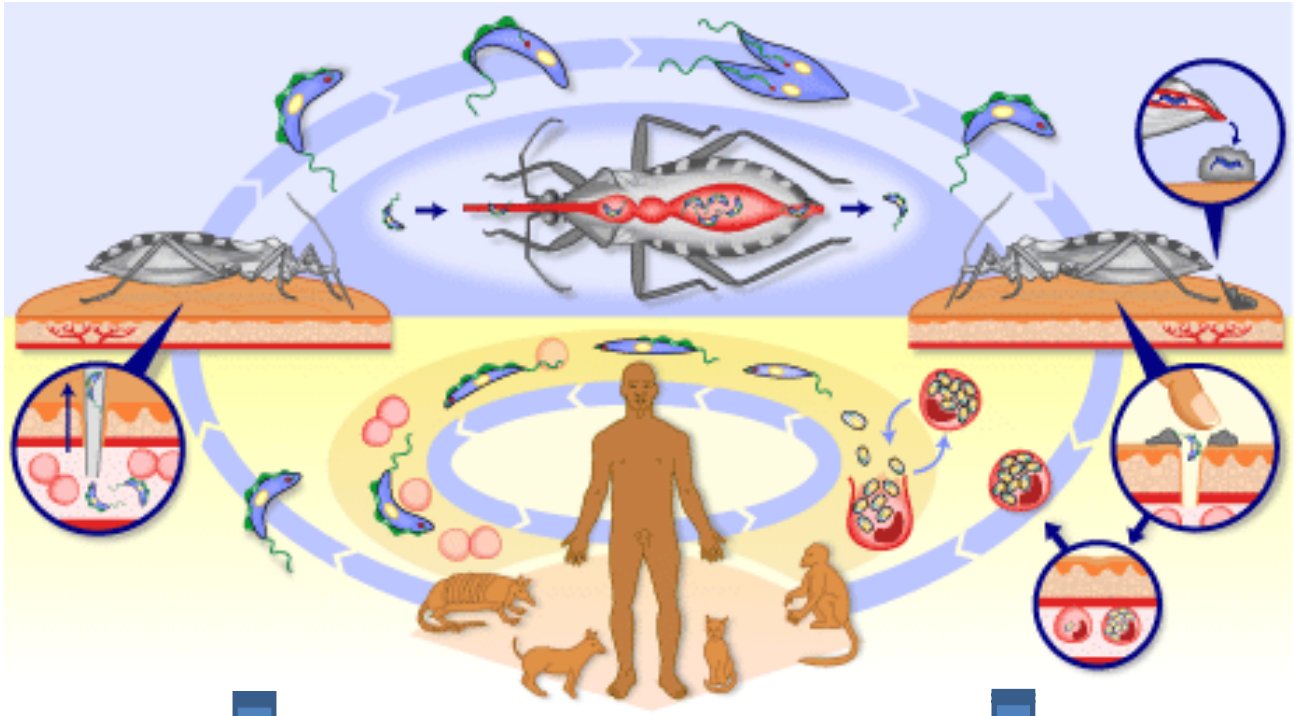


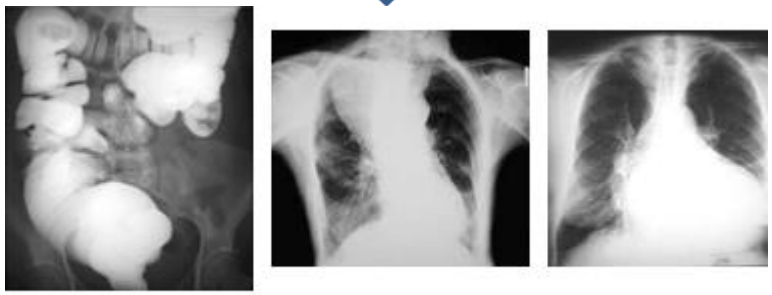
Clinical evolution of Chagas disease



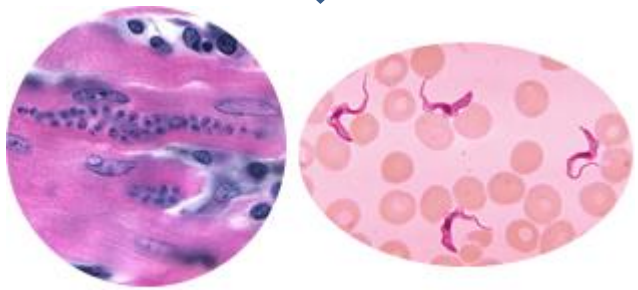
Mem Inst Oswaldo Cruz. 2009

Trypanosoma cruzi – Life cycle





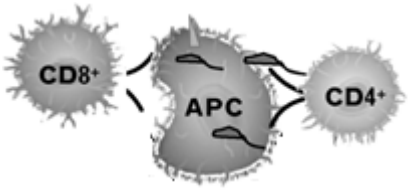
Chronic phase



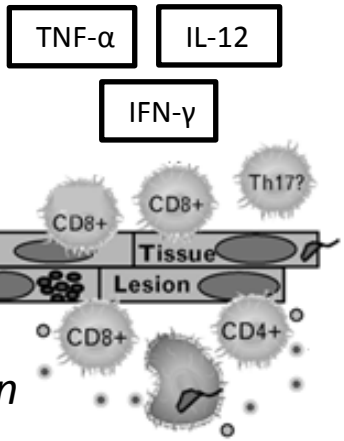
Acute phase

http://www.who.int/tdr/diseases/Chagas/lifecycle.htm.

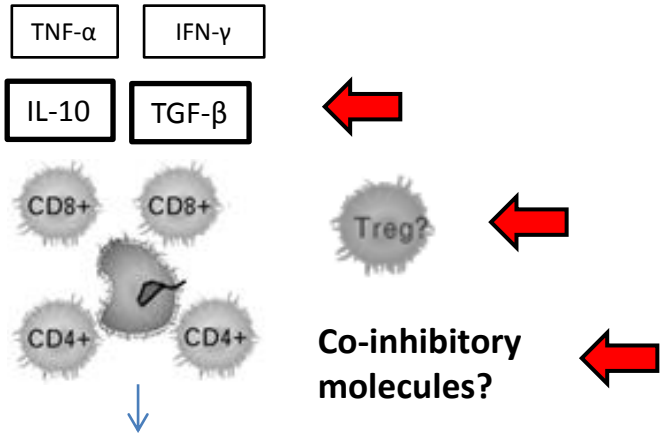
Inflammatory/anti-inflammatory immune response defines the outcome of *T. cruzi* infection



Acute phase

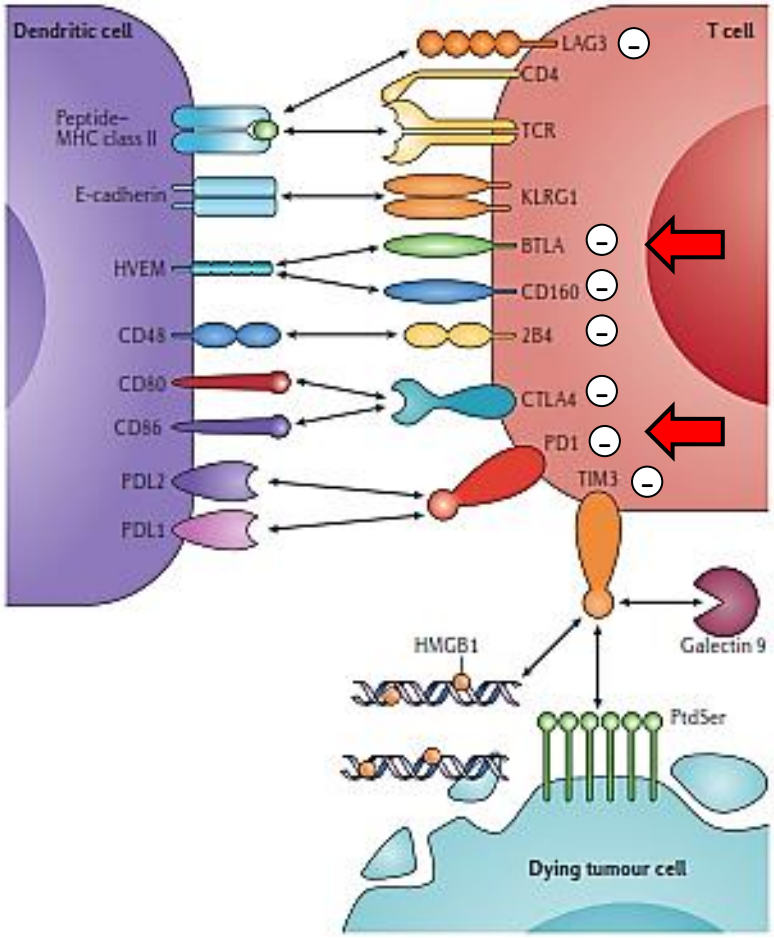


Inflammation



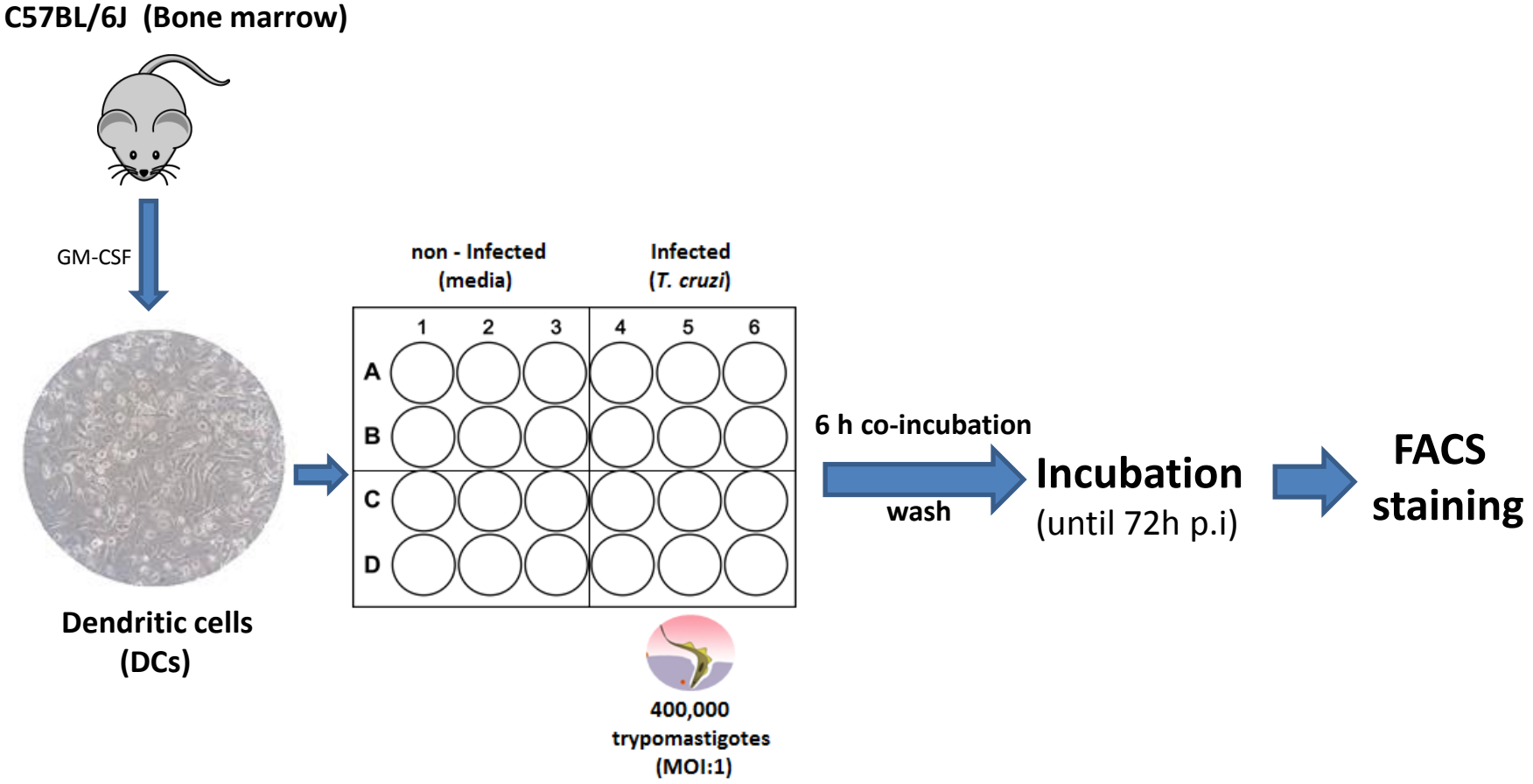
Chronic phase

Co-receptors that negatively regulate T cell function (Co-inhibitory pathways)

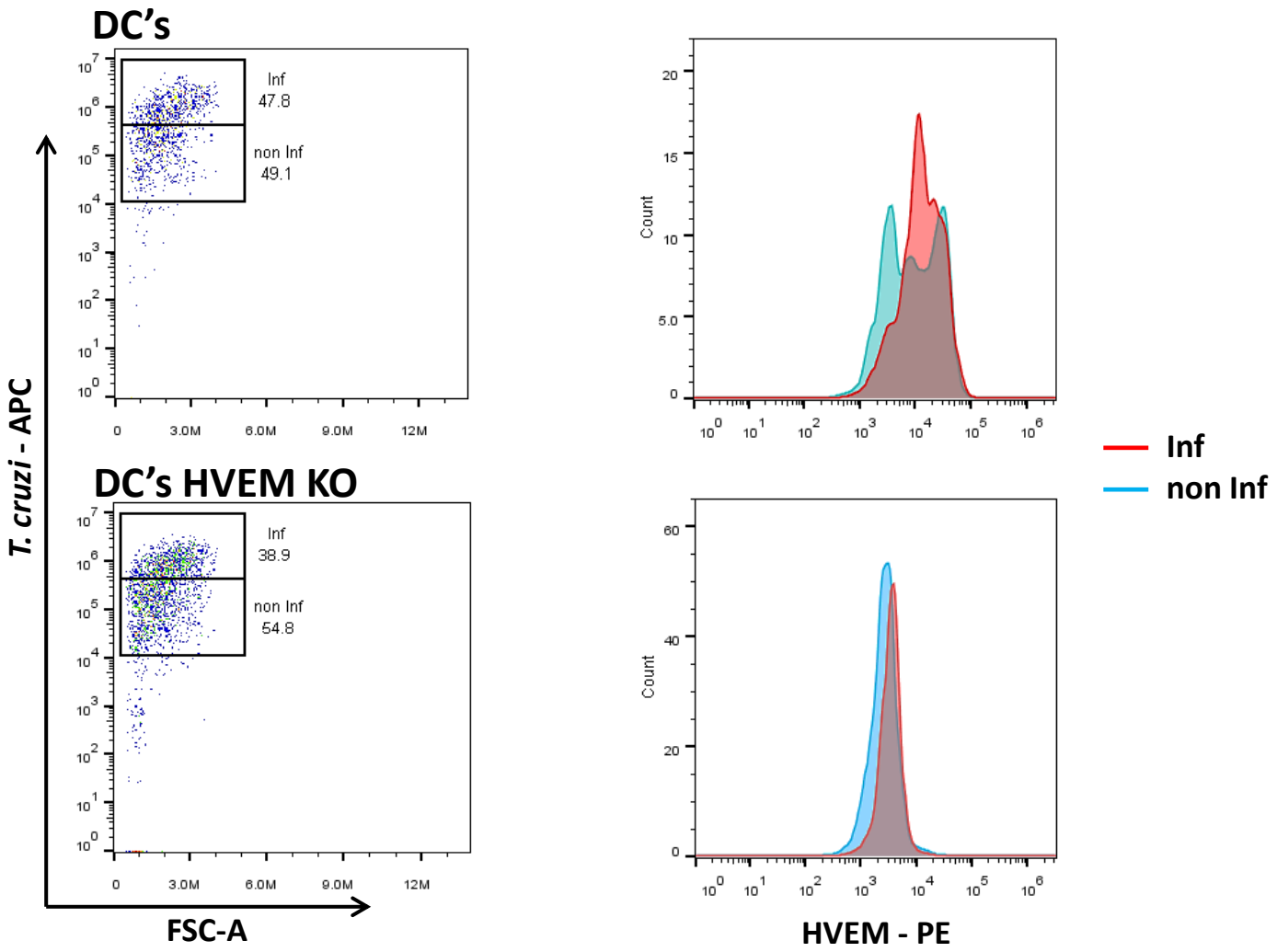


Nguyen, 2015. NATURE REVIEW | IMMUNOLOGY

T. cruzi induces expression of co-inhibitory molecules *in vitro*



T . cruzi induces the expression of HVEM in infected dendritic cells *in vitro*



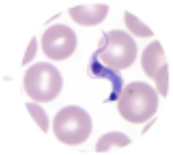
BTLA deficiency does not induce resistance to the *T. cruzi* infection *in vivo*

C57BL/6J
(7 weeks)

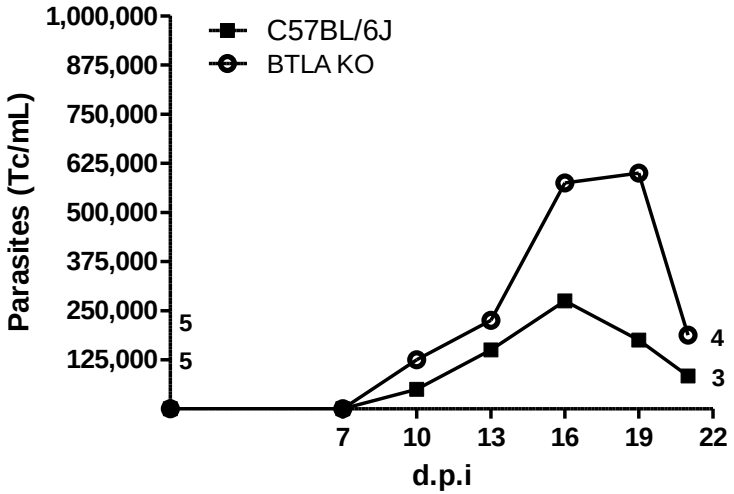
BTLA KO
(7 weeks)

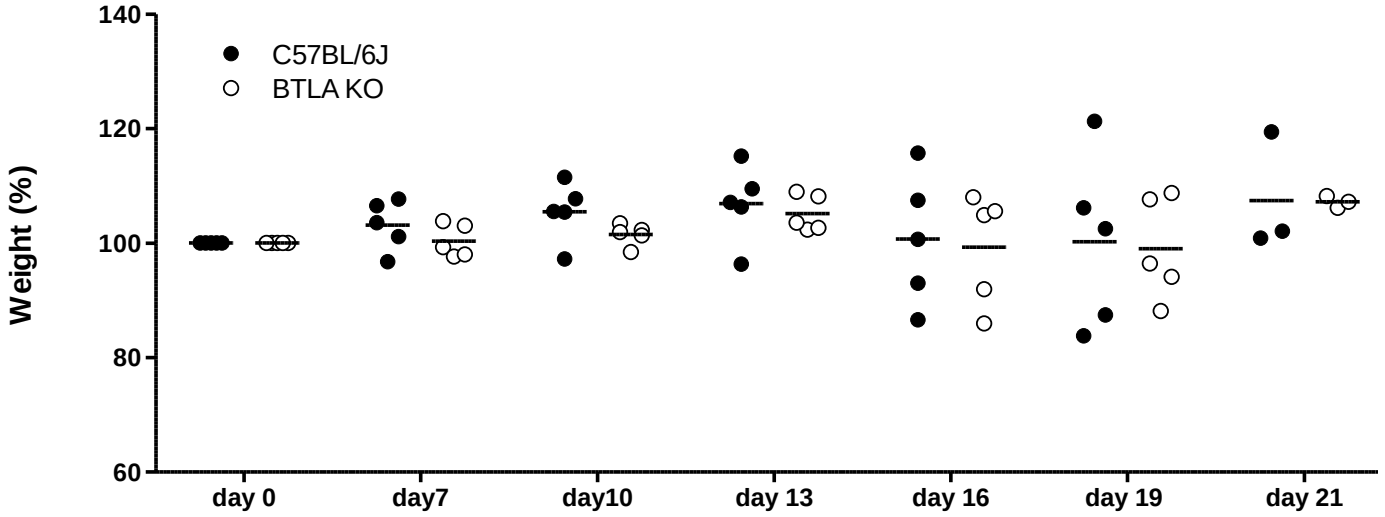
Parasitemia / Weight

Day 0

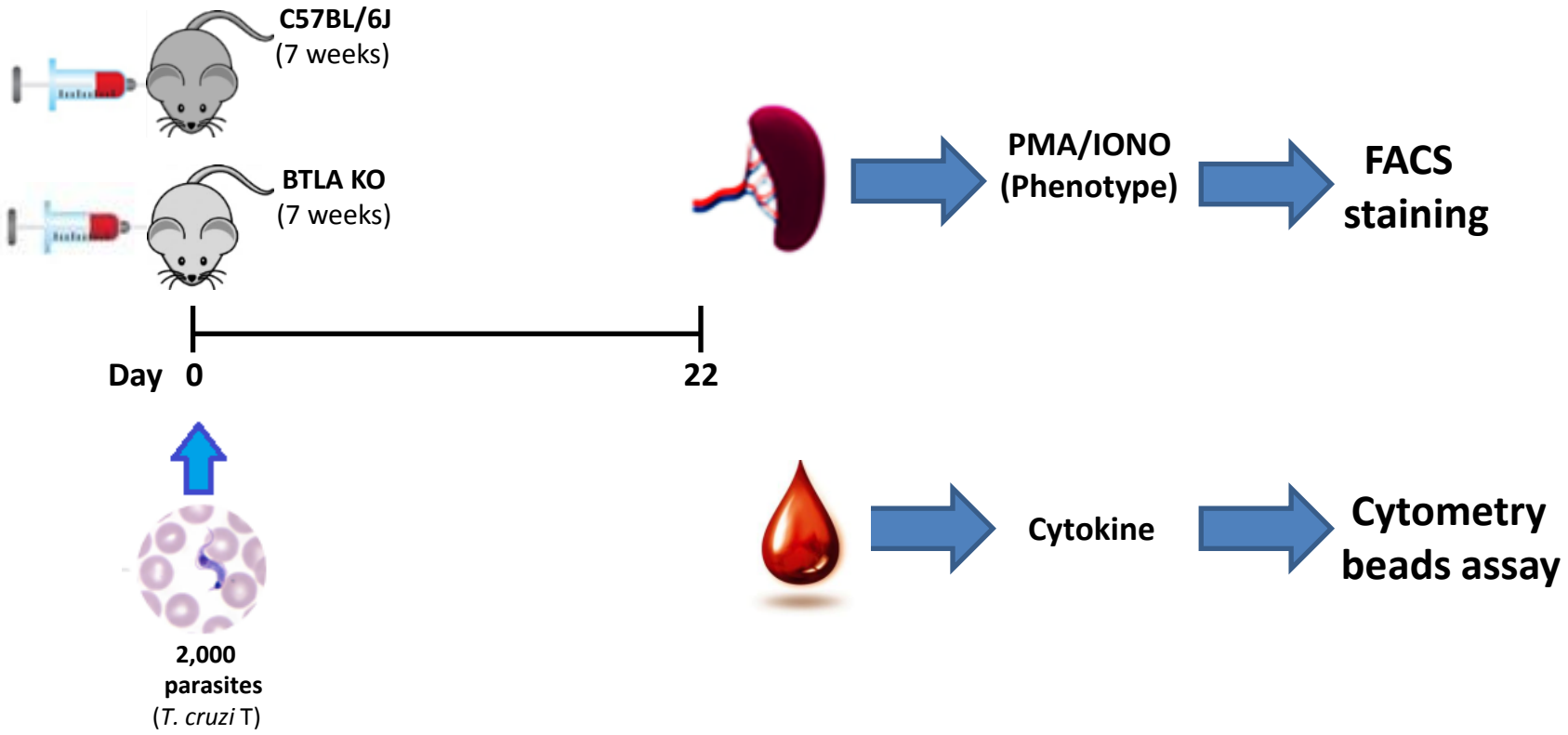


2,000 parasites
(*T. cruzi* T)

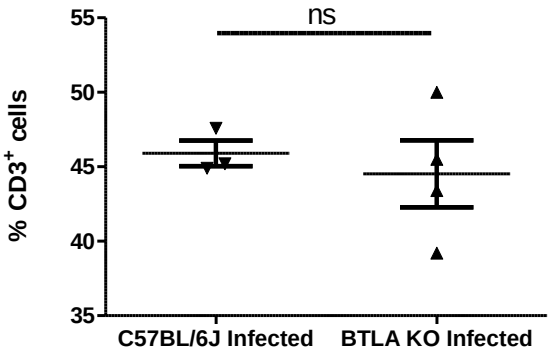


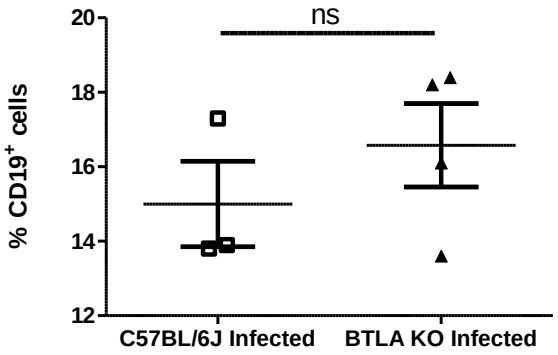


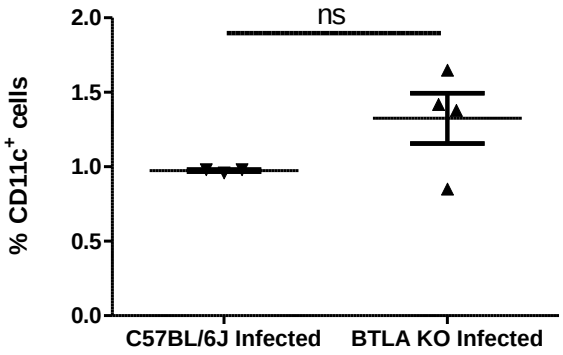
Effect of BTLA deficiency in the immune response during *T. cruzi* infection

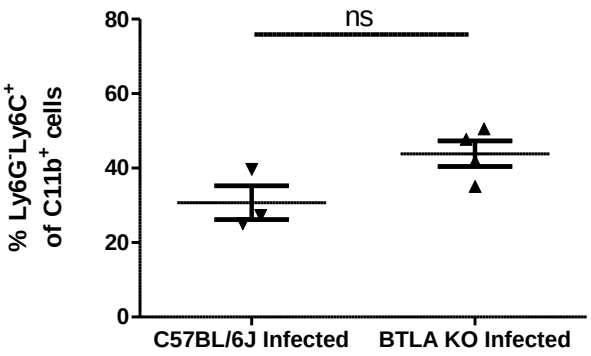


BTLA deficiency does not affect the frequency of different immune cell populations

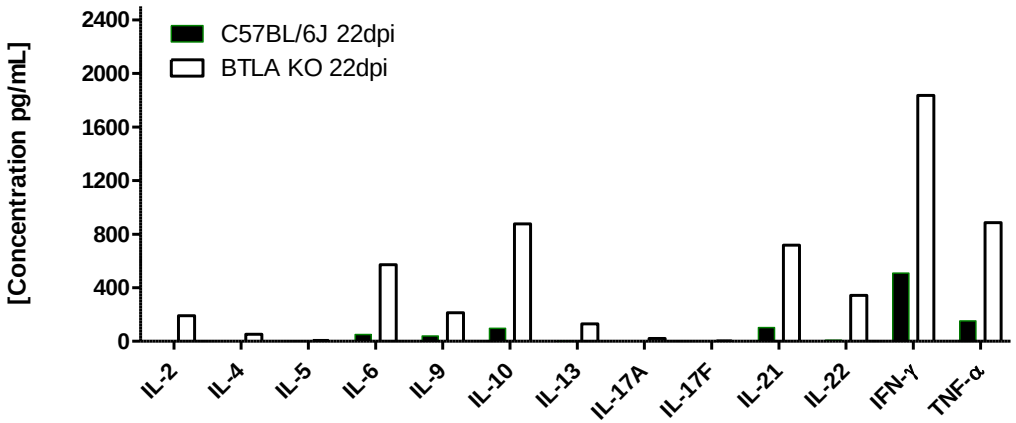




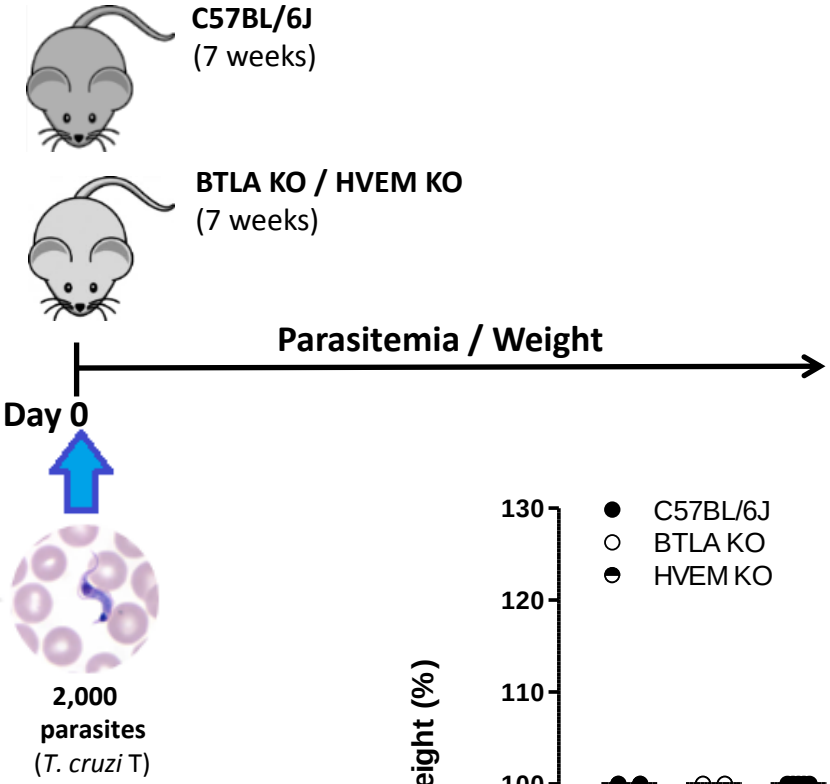


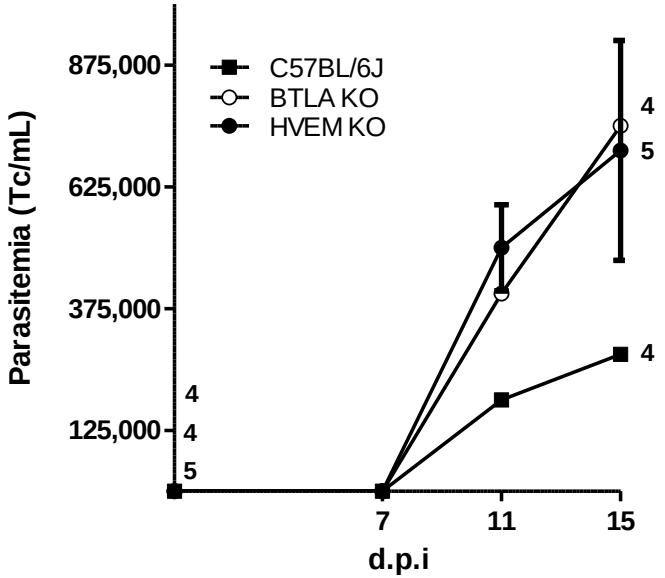


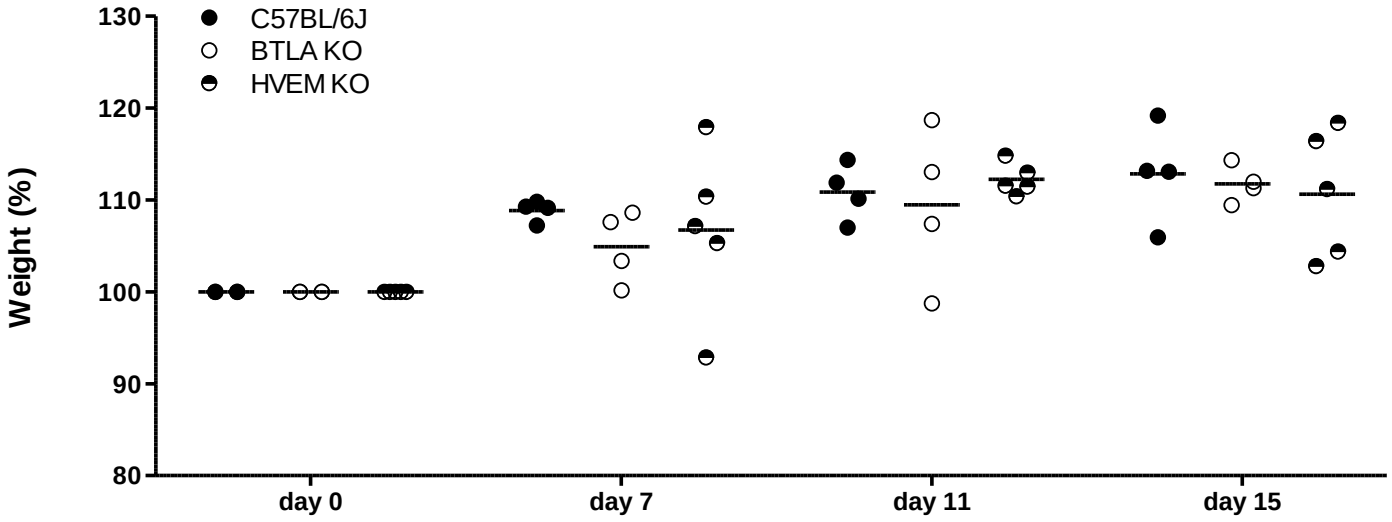
...but is accompanied by increased cytokine production



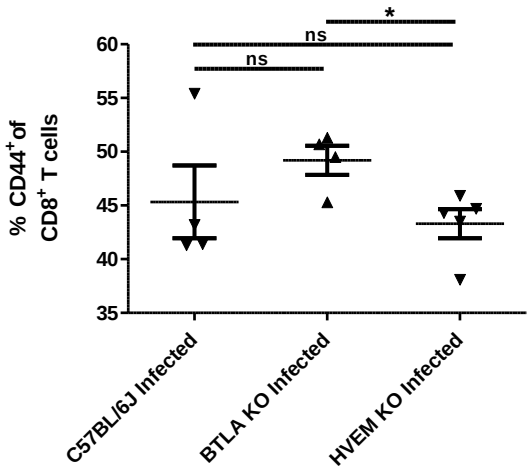
BTLA deficiency does not induce resistance to the *T. cruzi* infection *in vivo*

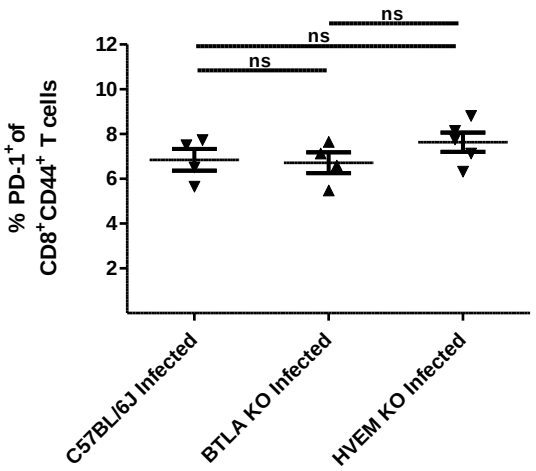


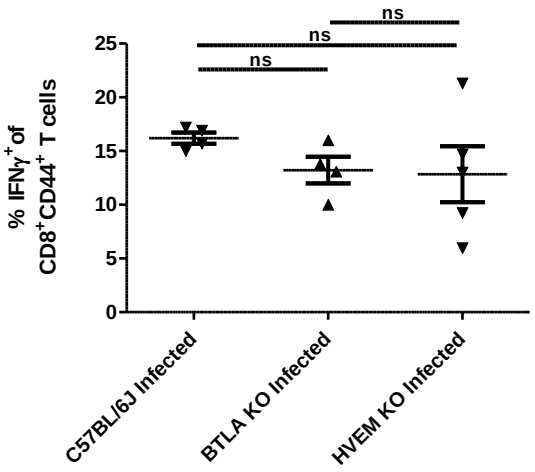


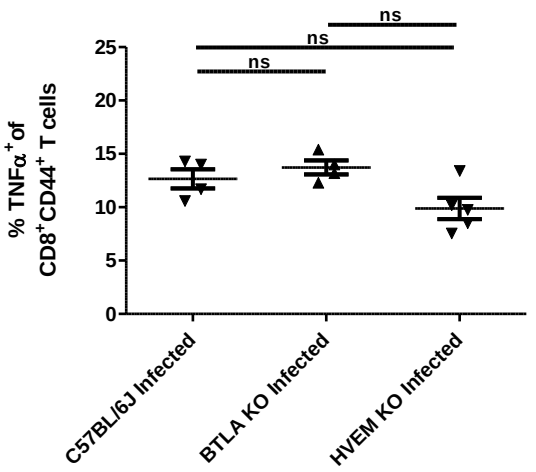


BTLA deficiency does not enhance T cell activation or its effector function

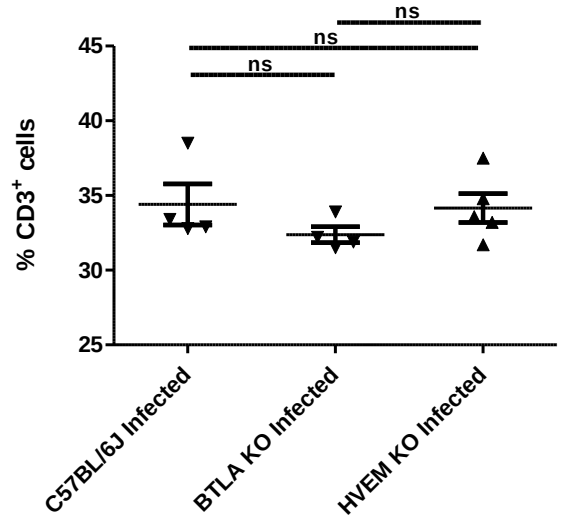


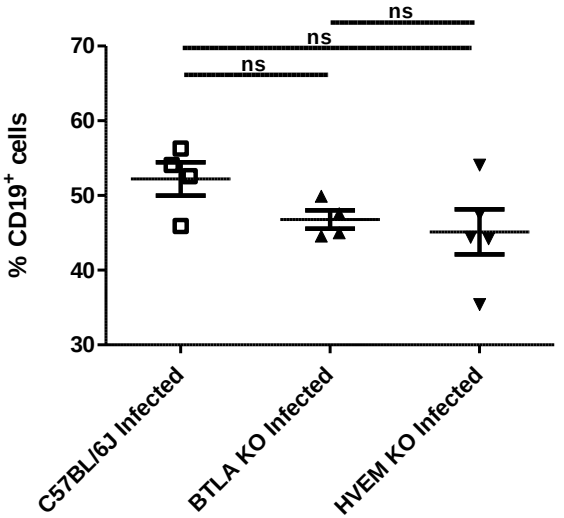


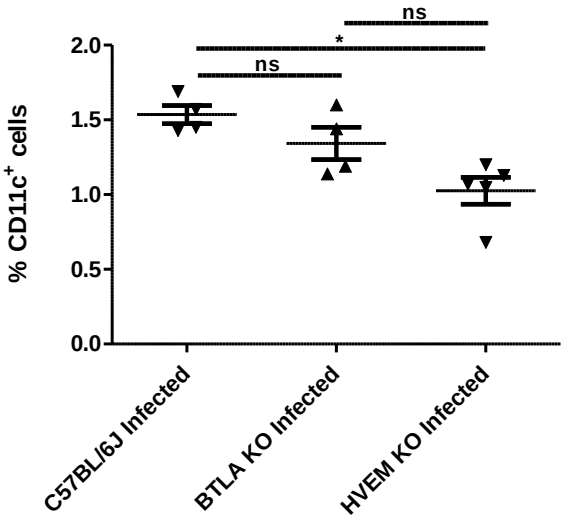


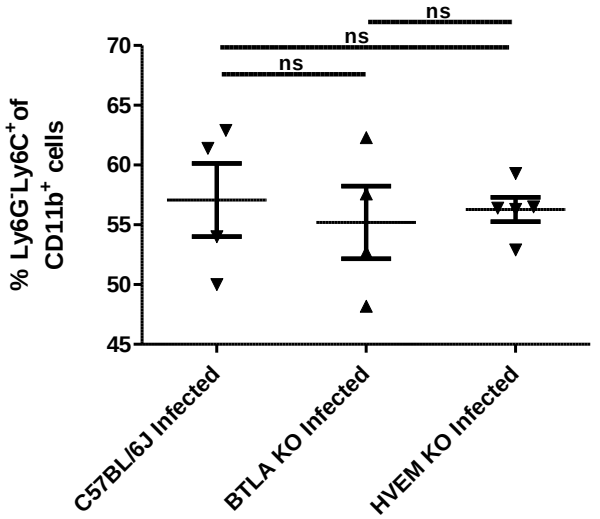


BTLA deficiency does not affect the frequency of different immune cell populations

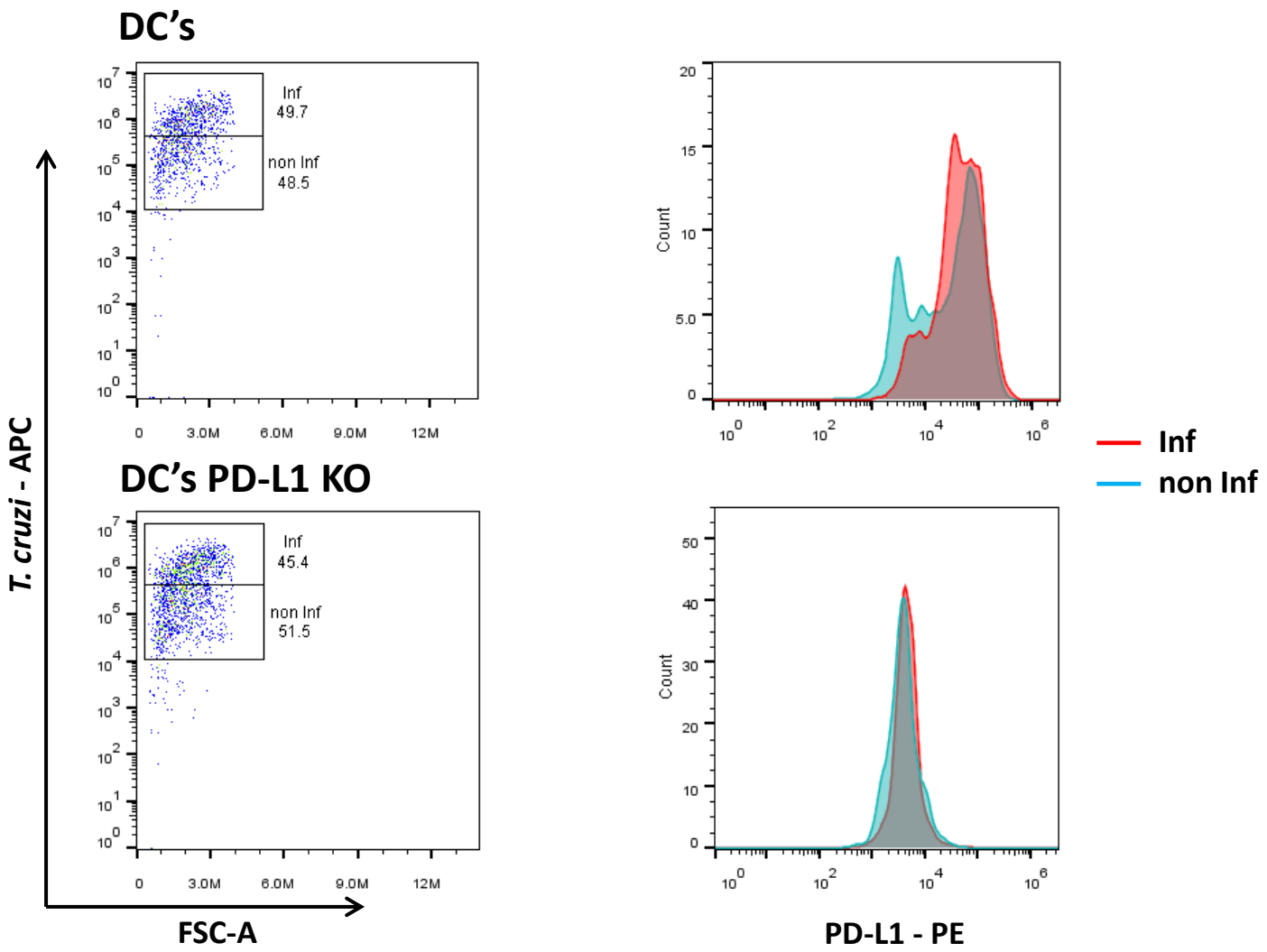








T . cruzi induces the expression of PD-L1 in infected dendritic cells *in vitro*



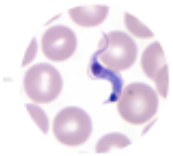
PD-L1 deficiency does not induce resistance to the *T. cruzi* infection *in vivo*

C57BL/6J
(7 weeks)

PD-L1 KO
(7 weeks)

Parasitemia / Weight

Day 0



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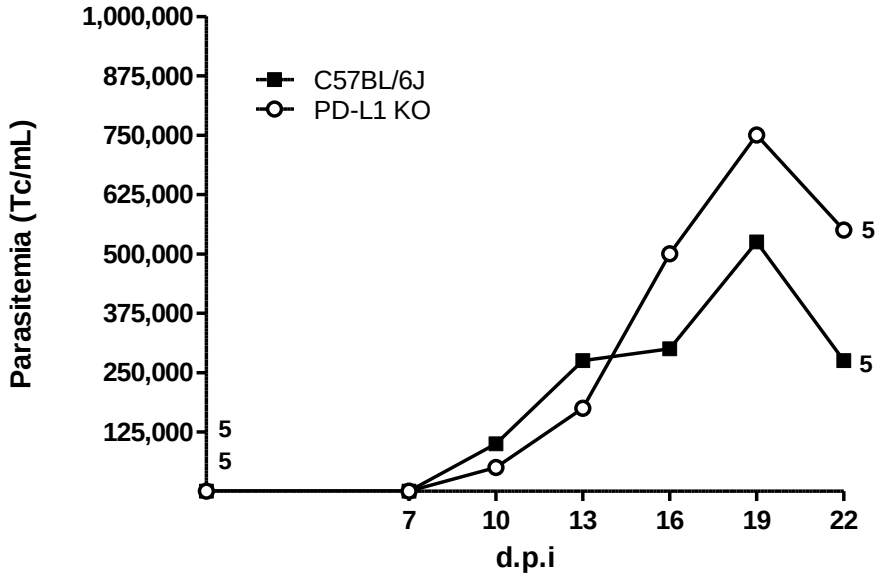
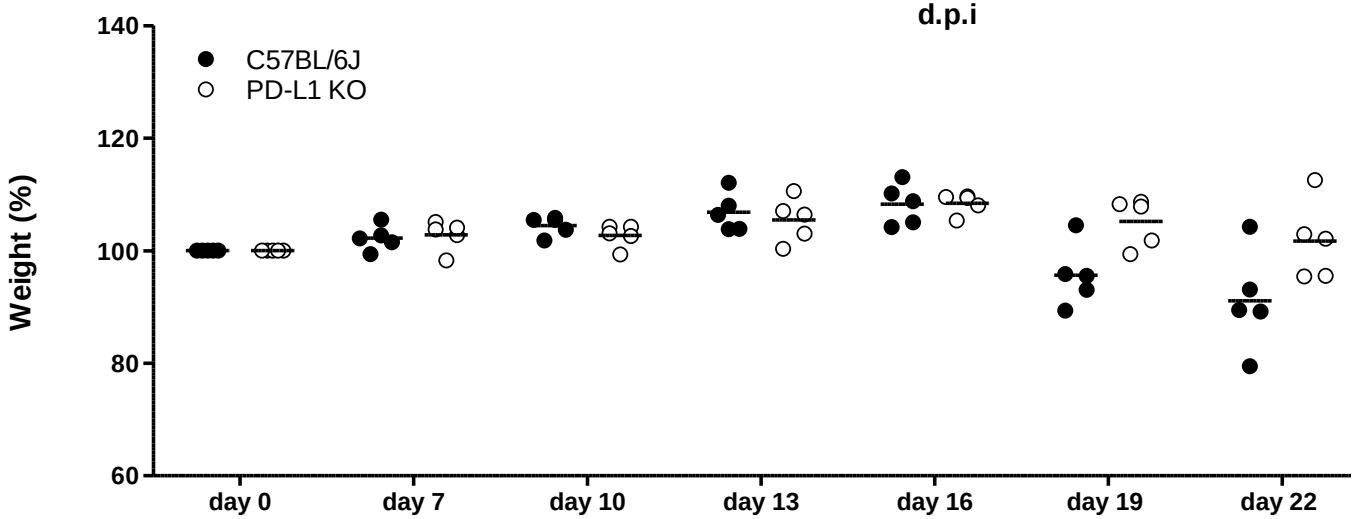
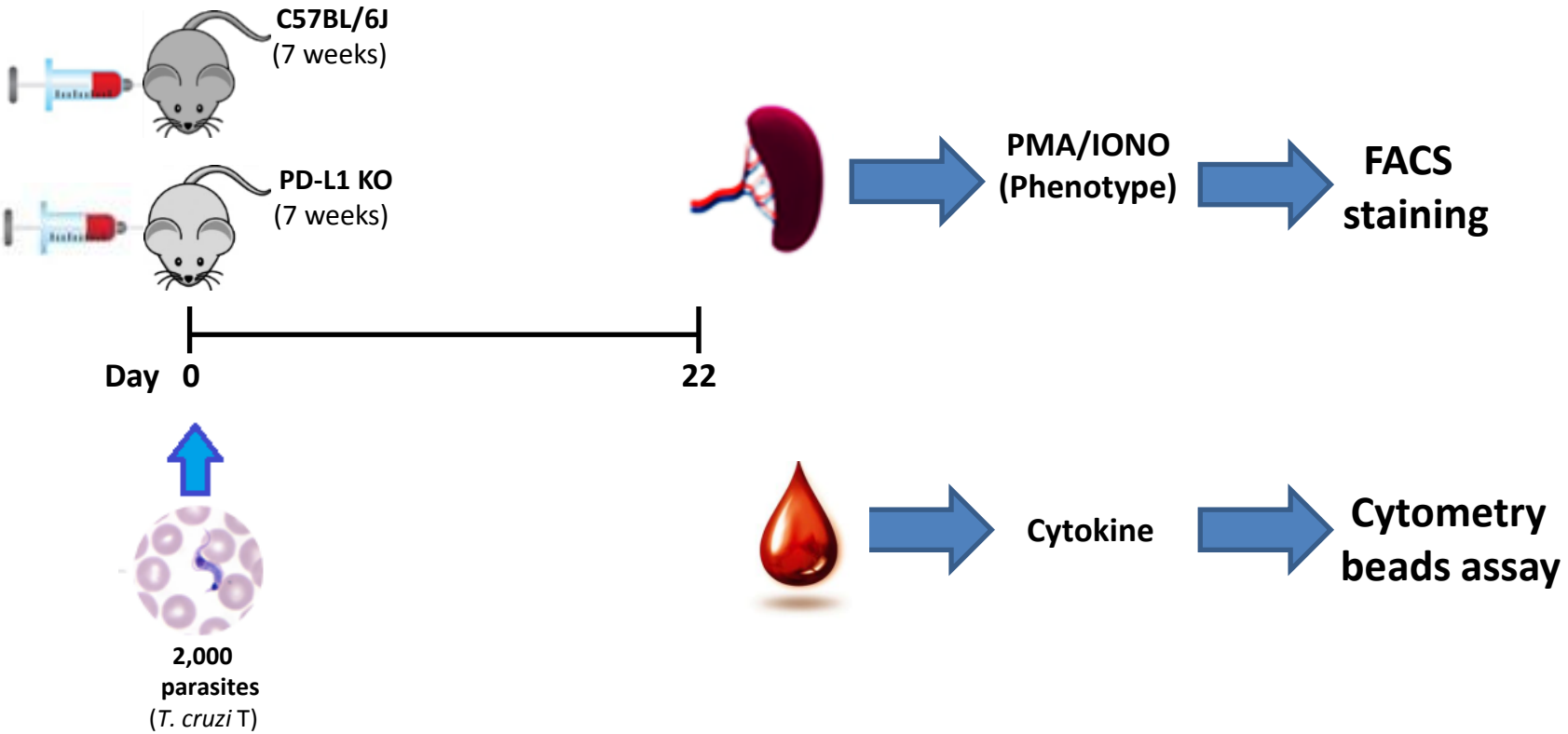
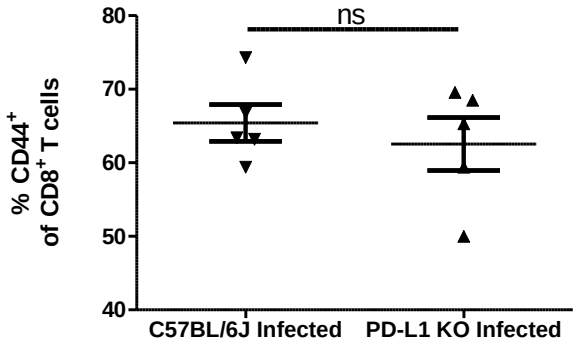


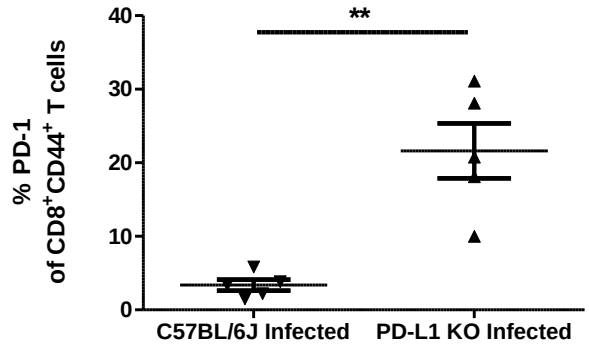


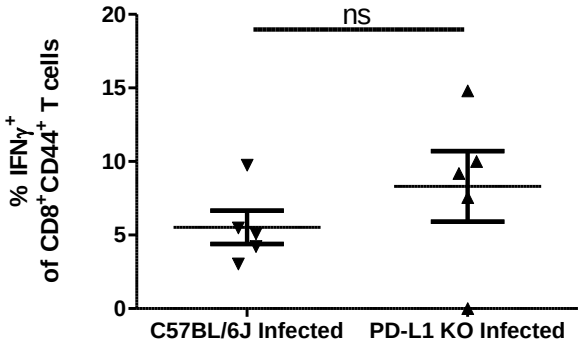
Effect of PD-L1 deficiency in the immune response during *T. cruzi* infection

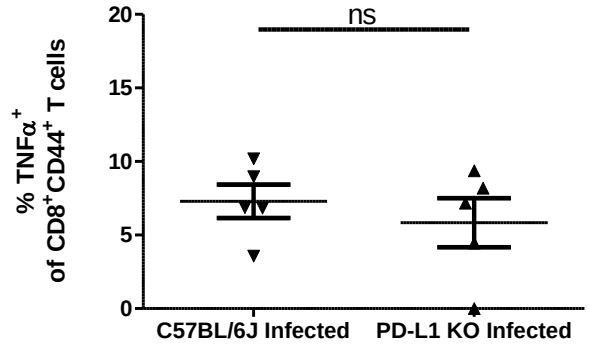


PD-L1 deficiency does not enhance T cell activation or its effector function but exhibits significate co-inhibitors expression

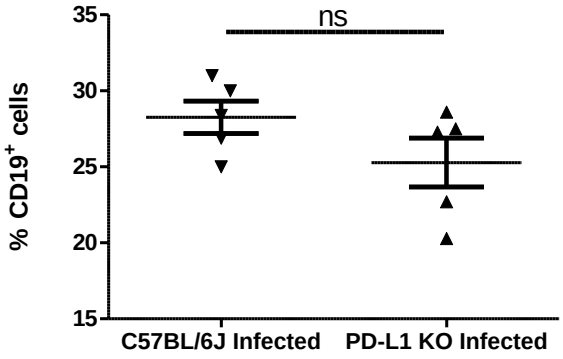


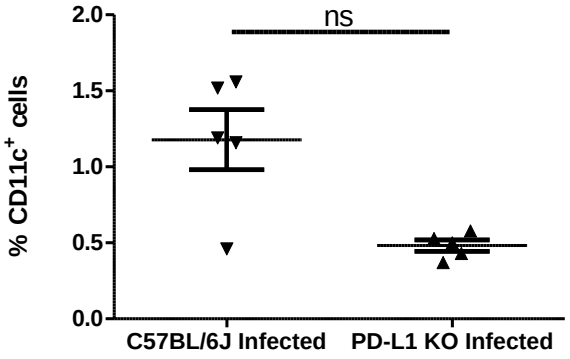


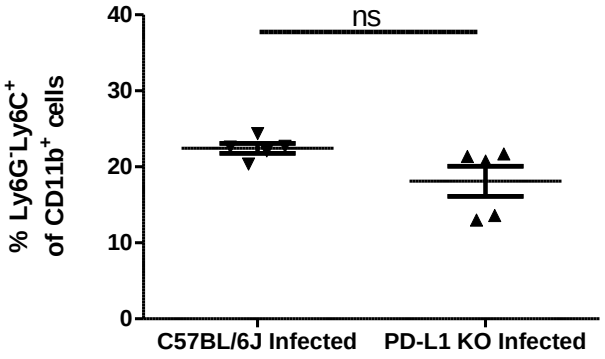




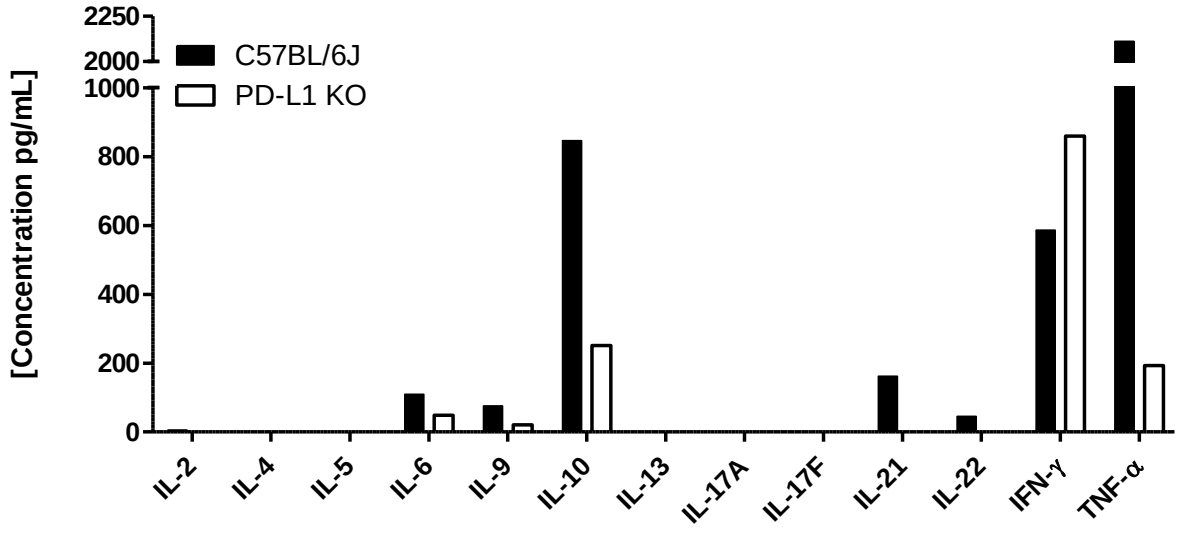
PD-L1 deficiency does not affect the frequency of different immune cell populations





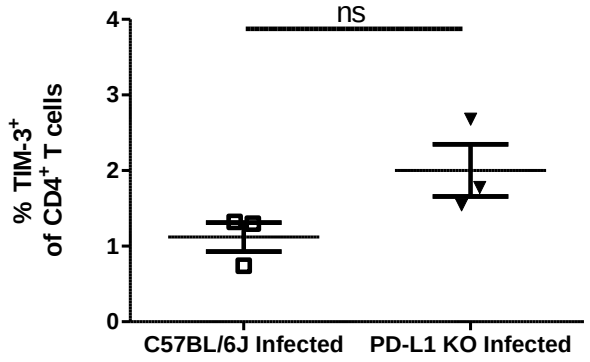


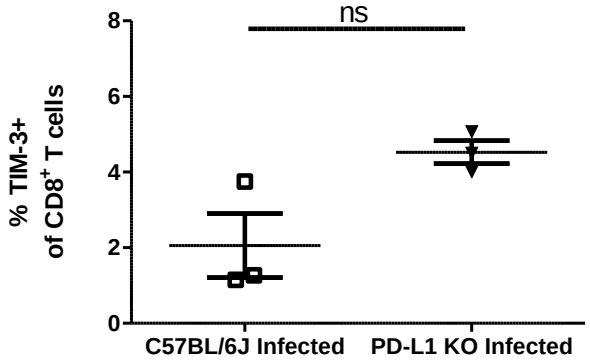
...and does not improve the cytokine production



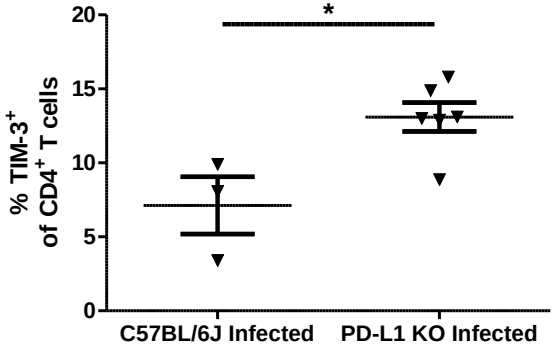
Interruption of PD-1:PD-L1 pathway induces TIM-3 upregulation during *T. cruzi* infection

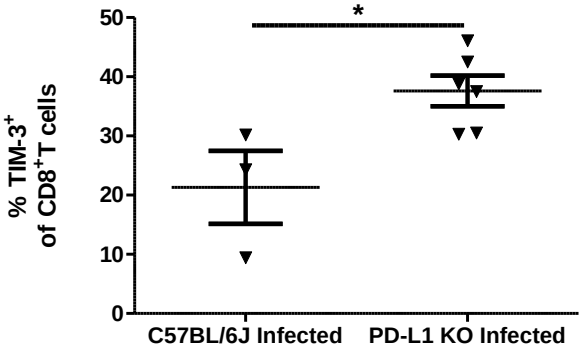
At 10 dpi





At 22 dpi





Summary

- BTLA:HVEM and PD-1:PD-L1 co-inhibitory pathways play an important role in the control of the parasite during the infection by *T. cruzi* Tulahuen strain.

- Interruption of both co-inhibitory pathways do not improve the resistance to infection but would also favor a pronounced exhaustion stage of immune cells.

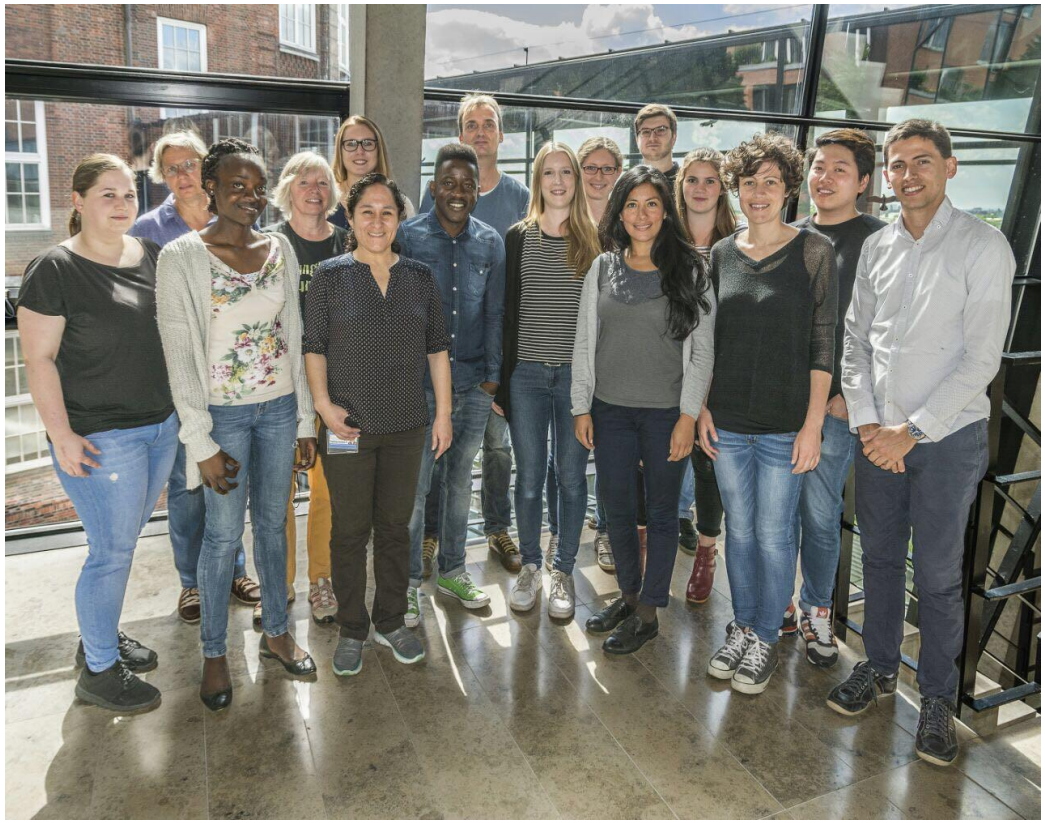
- BTLA and PD-L1 deficiency does not alter the frequencies of immune cell population suggesting the existence the other immunosuppressive mechanisms (inhibitory receptors, suppressor cytokines)

- TIM-3 expression is upregulated upon PD-1:PD-L1 pathway disruption suggesting a compensatory mechanism sustaining the exhaustion status of T cells.

Outlooks

- Develop a TIM-3 blocking antibody treatment in mice.
- Develop dual blockade assays employing antibodies against PD-1 and TIM-3 in mice .
- Evaluate other inhibitory molecules (2B4, TIGIT) as potential candidates for infection control.

Acknowledgments



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PD. Dr. Eva Tolosa

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