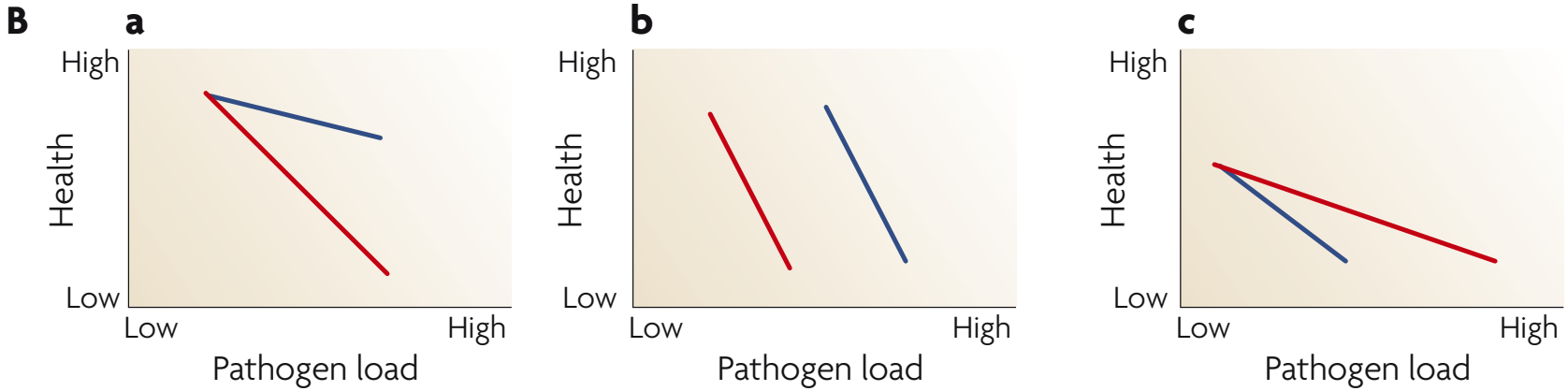
BIO-479

Disease Tolerance as a Defense Strategy

2022/09/29

Resistance and tolerance upon infection

- Resistance: A host has evolved mechanisms to kill and eliminate a pathogen to promote health from infection.
- Tolerance: A host can also limit the damage that is induced by the pathogen.

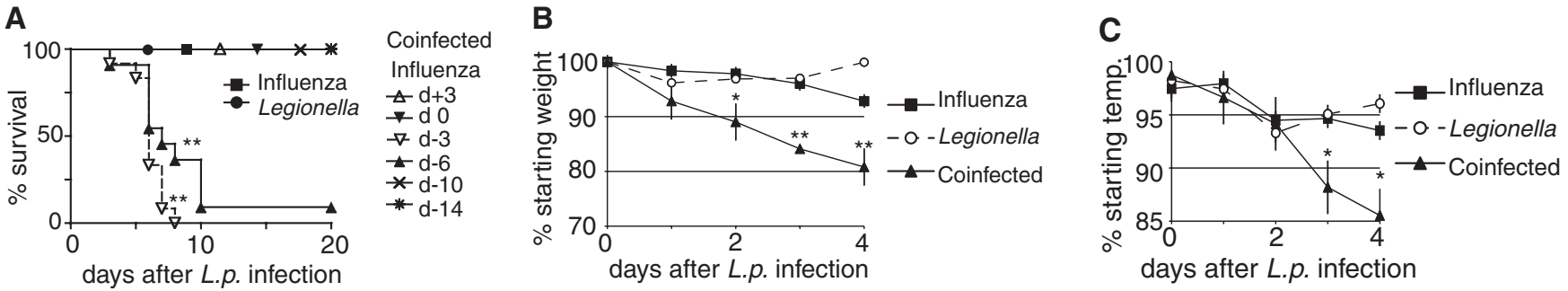


Schneider et al., Nat Immunol 2008

Viral-bacterial co-infections

You do an internship in a laboratory focused on understanding pathomechanisms of infectious disease. Your PI asked you to test a model of viral and bacterial co-infections using influenza virus and Legionella pneumophila, respectively. After testing several conditions of co-infections you make the following observations concerning animal survival (see below).

(1) Interpret the results!
(2) What conclusion can you draw regarding the timing of viral infection?



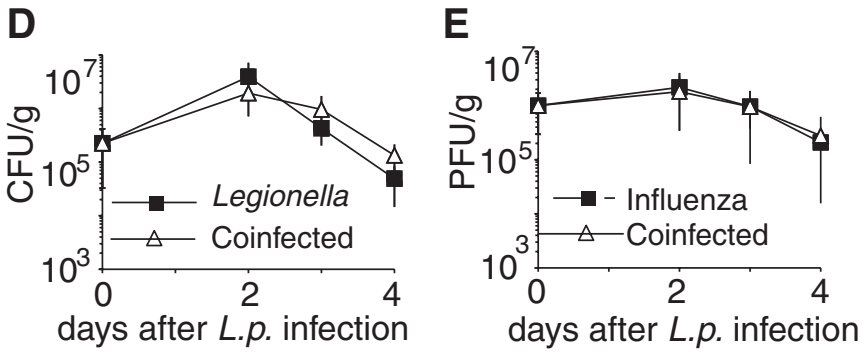
Viral-bacterial co-infections

- An established viral infection is essential for lethality, while a resolved infection with Influenza virus no longer affected the ability of mice to clear the infection.
- Co-infected mice featured multiple signs of severe disease, including body weight changes, decreased temperature.

You are tasked to measure pathogen burden in the deceased animals. Measuring viral and bacterial loads you measure the following effects (see below).

(1) Describe the results!

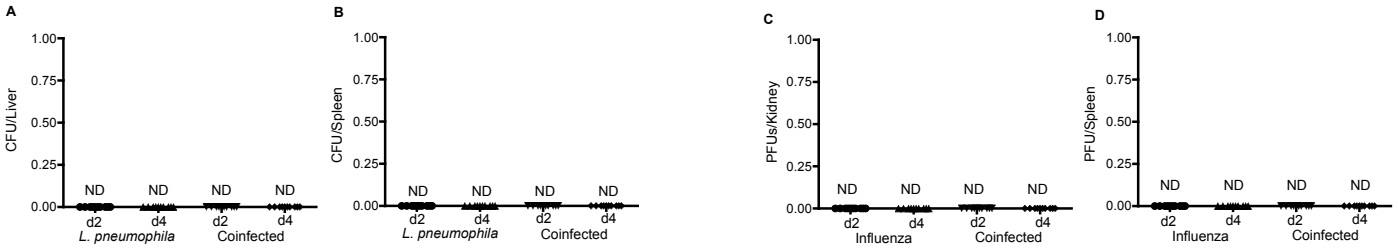
Despite a notable difference in animal survival, the pathogen burden between singly infected and co-infected animals is the same.



Viral-bacterial co-infections

You presented the findings in your weekly lab meeting. A senior colleague is not yet fully convinced that there is no difference in pathogen burden. You were prepared for such concerns and showed additional results that corroborate your initial conclusion.

(1) Explain what additional data you might have collected!



There was no systemic dissemination of influenza or *Pneumophila* after co-infection.

Lethal synergy between influenza and Pneumophilia infection is not due to impaired resistance to either pathogen!

Viral-bacterial co-infections

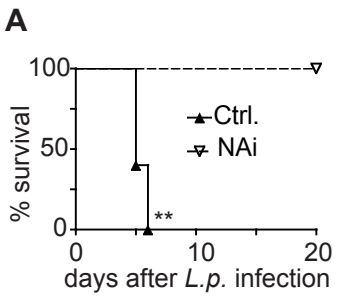
You wonder whether intact virions were necessary to trigger synergistic lethality in these mice.

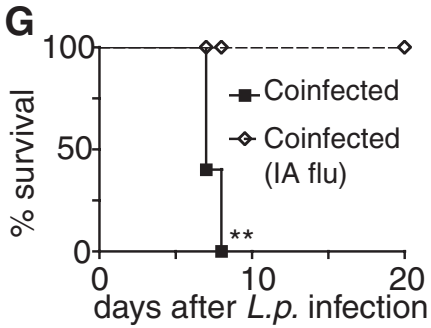
(1) Describe how you could test this hypothesis!

- Inactivation of the virus (IR, Formalin)
- Treatment with an antiviral (neuraminidase inhibitor)

(2) What is your conclusion?

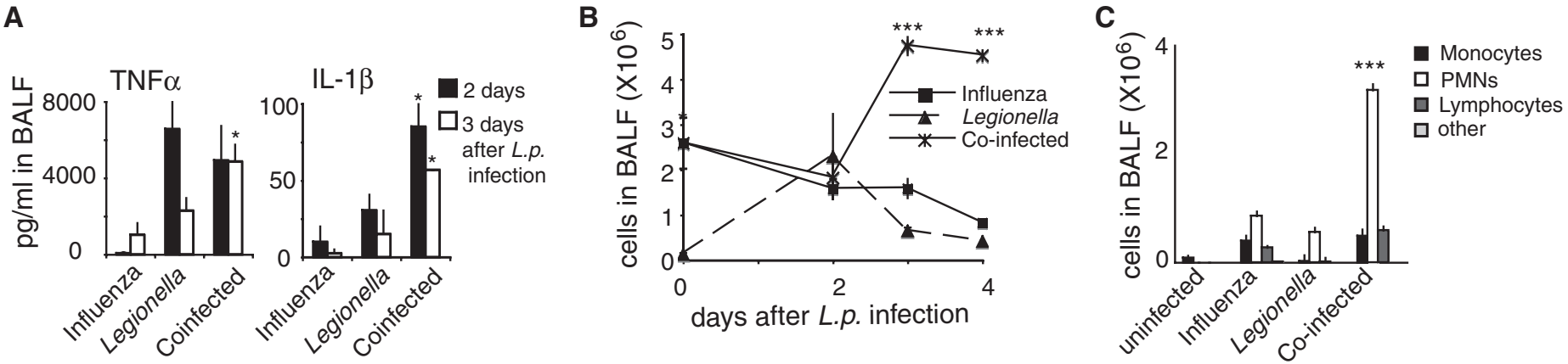
Productive viral infection is necessary to induce systemic lethality!





Viral-bacterial co-infections

After discussion with your PI, you think that there might be an excessive inflammatory response triggered by co-infection!
(1) What type of analysis would you like to perform to investigate this idea?



(2) Describe the findings and make a conclusion!

Viral-bacterial co-infections

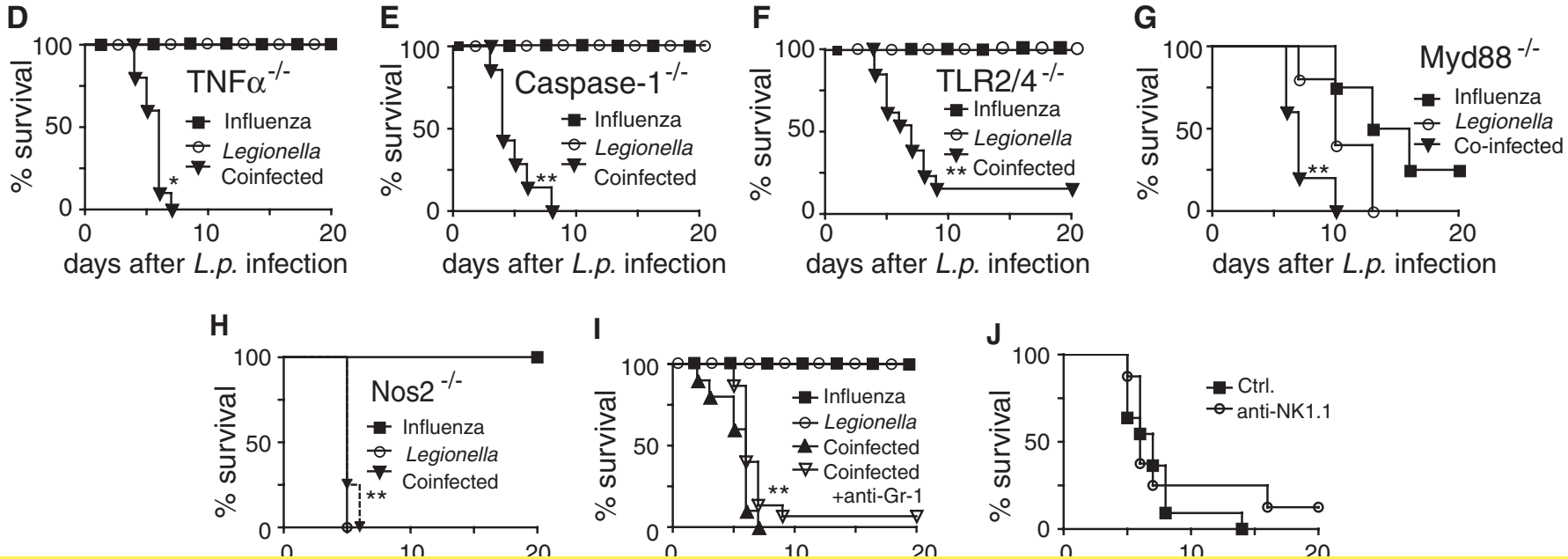
You noted an increased expression of pro-inflammatory cytokines in the lung tissue and BALF and concomitantly an increase in inflammatory cells in co-infected mice compared to singly infected mice. Therefore, you next ask whether ablating the host immune response might be responsible for triggering synthetic lethality.

(1) List experimental measures by which you could interfere into the host immune response!

- Genetic knockout of pattern-recognition receptors or essential adaptor proteins (e.g., TLR2/4)
- Anti-cytokine treatment (e.g., anti-TNFa)
- Depletion of relevant immune cell populations
- Immunocompromised mice (e.g., Rag2 KO mice)
- Systemic immunosuppressive therapy (Dexamethason)

Viral-bacterial co-infections

After several weeks of experimentation, you have acquired the following results.
(1) Describe and conclude!

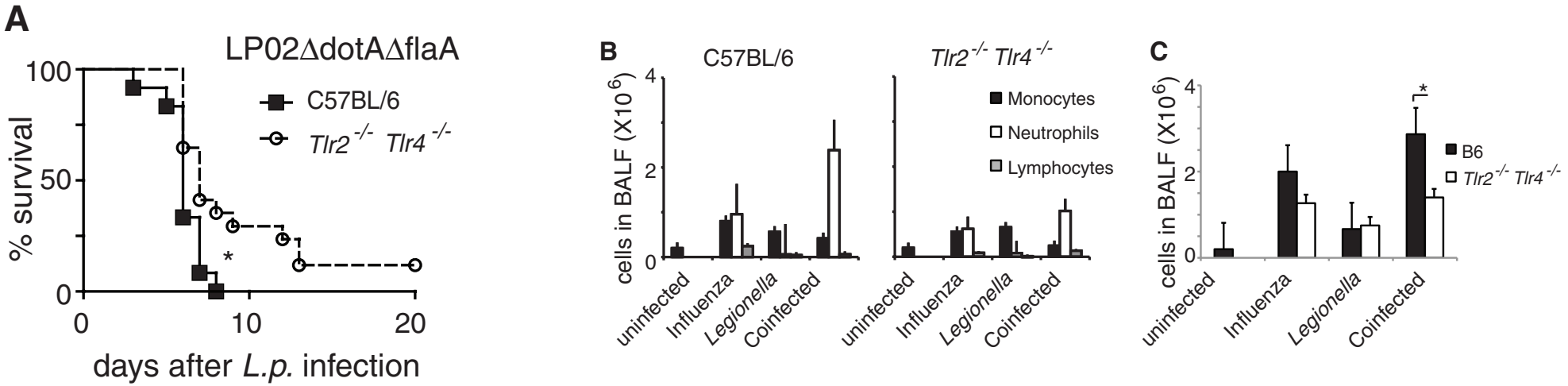


Elimination of all major immune pathways does not rescue from lethal synergy. Therefore, the lethal outcome is not solely due to excessive inflammatory response or immunopathology.

Viral-bacterial co-infections

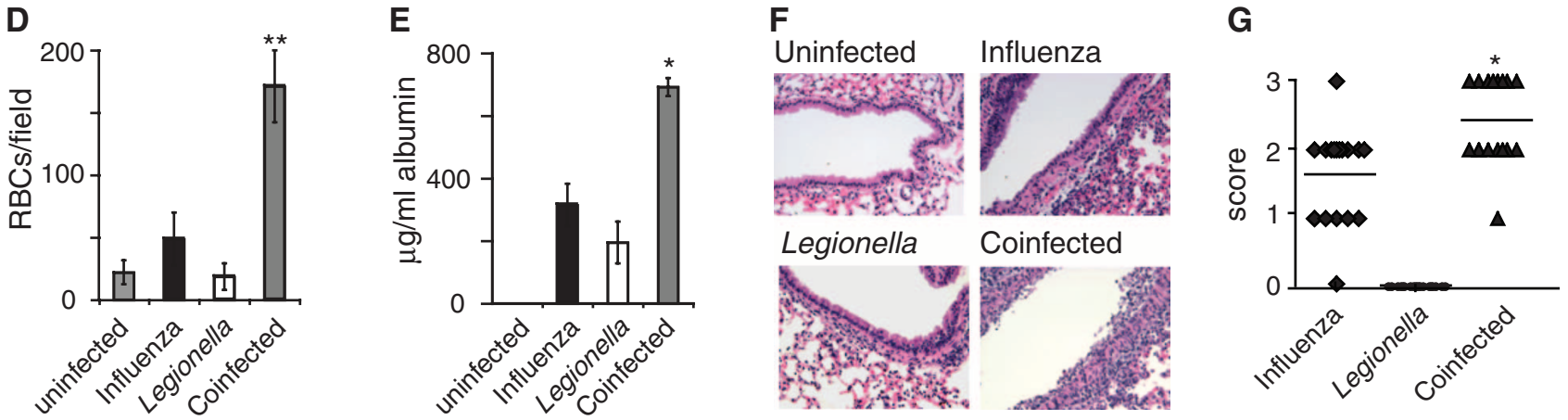
As a final consideration, you tested whether synergistic lethality could also be triggered by a severely attenuated strain of *Legionella pneumophila*!

(1) Describe the results!



Viral-bacterial co-infections

Your left with the thought that lethal synergy might be caused by failed tolerance to tissue damage!
(1) What analyses would you like to perform to test this idea?



(2) Describe and interpret the results!

Viral-bacterial co-infections

Following these results you search the literature for factors that might be able to attenuate the tissue damage response. You find the following paper abstract:

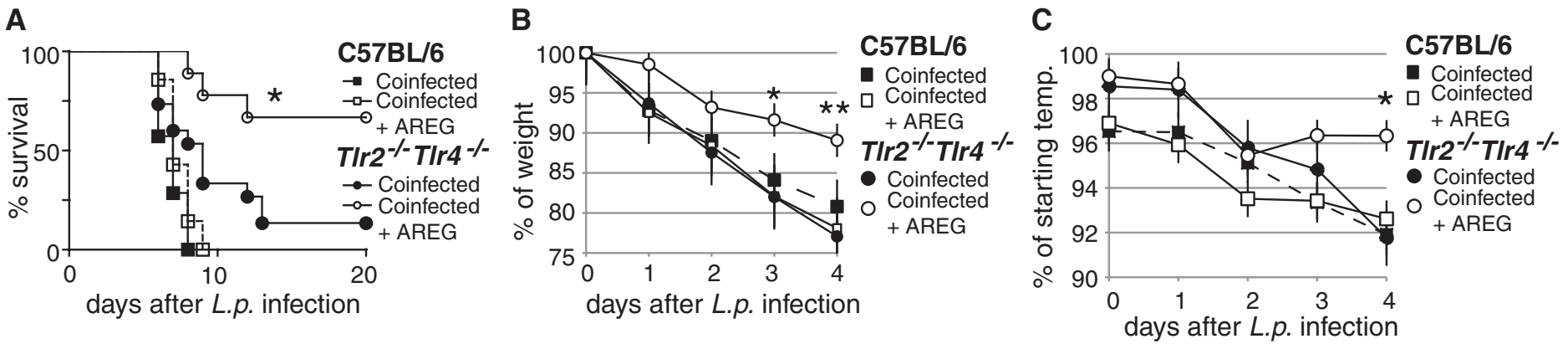
Abstract

Innate lymphoid cells (ILCs), a heterogeneous cell population, are critical in orchestrating immunity and inflammation in the intestine, but whether ILCs influence immune responses or tissue homeostasis at other mucosal sites remains poorly characterized. Here we identify a population of lung-resident ILCs in mice and humans that expressed the alloantigen Thy-1 (CD90), interleukin 2 (IL-2) receptor a-chain (CD25), IL-7 receptor a-chain (CD127) and the IL-33 receptor subunit T1-ST2. Notably, mouse ILCs accumulated in the lung after infection with influenza virus, and depletior of ILCs resulted in loss of airway epithelial integrity, diminished lung function and impaired airway remodeling. These defects were restored by administration of the lung ILC product amphiregulin. Collectively, our results demonstrate a critical role for lung ILCs in restoring airway epithelial integrity and tissue homeostasis after infection with influenza virus.

(1) Based on the conclusion of the paper, what would you test next?

Viral-bacterial co-infections

You test the effects of administration of amphiregulin (AREG) and make the following observations:



(1) Describe and interpret the results!
(2) What would you like to test next?

Viral-bacterial co-infections

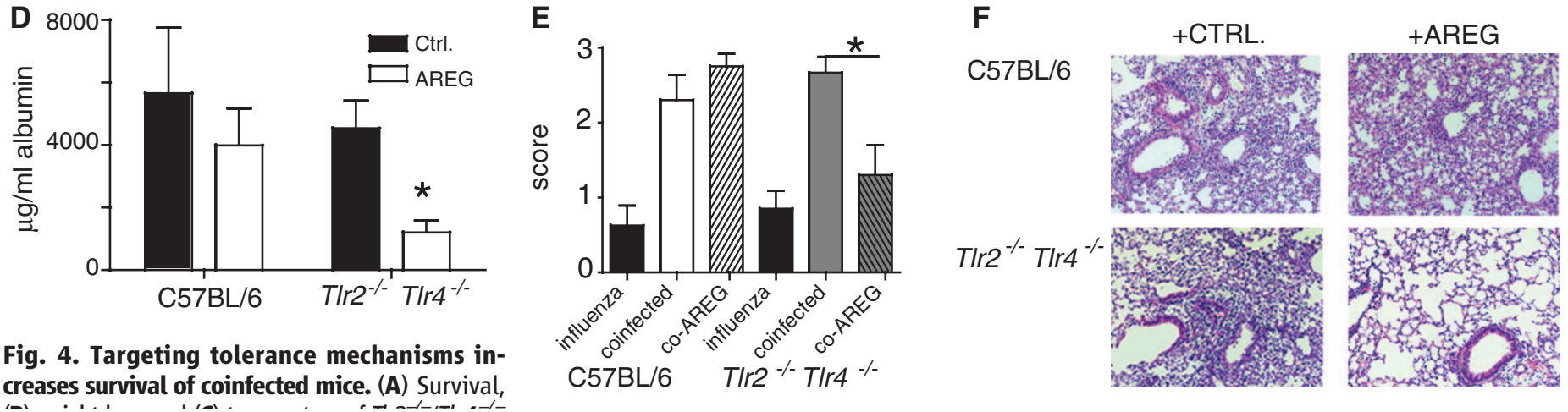
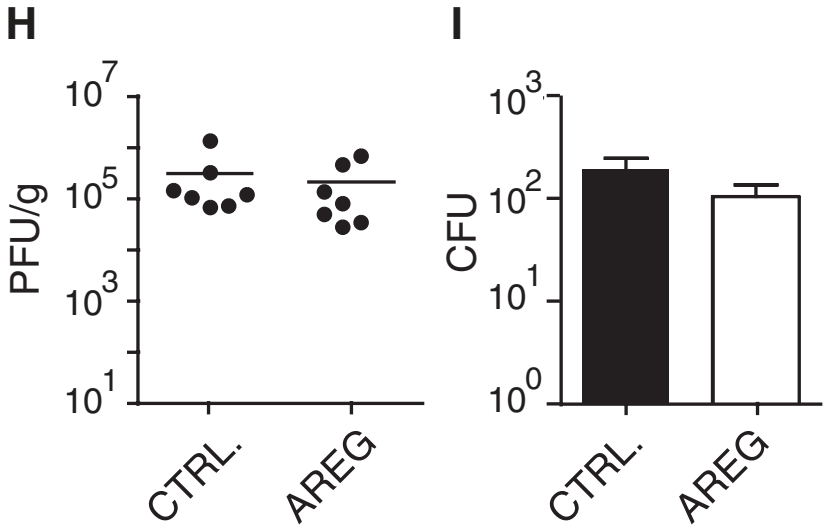


Fig. 4. Targeting tolerance mechanisms increases survival of coinfected mice. (**A**) Survival,

(1) Describe and interpret the results!
(2) What additional measurement is necessary to conclude no impact on resistance?

Viral-bacterial co-infections



(1) Describe and conclude!

Viral-bacterial co-infections

Summary:
- Lethal synergy between bacterial and viral co-infections can results from loss of tolerance to infection-induced tissue damage.
- Morbidity and mortality form co-infection is independent of pathogen burden and the inflammatory host response
- Promoting tissue repair can be a strategy to mitigate the severity of illness caused by bacterial and viral co-infection

General questions

1. Briefly, explain what is meant by disease tolerance to infection. Given a concrete example to illustrate the difference between tolerance and resistance other than the one mentioned in the manuscript (Tip: check the 1st paragraph/page of the further reading article).
2. Influenza virus can decrease the immune response to bacterial infection – can you search for one possible explanation?
3. Describe briefly the disease that results from Legionella pneumophila infection!

Questions related to the manuscript

1. Fig-1: Explain how a neuraminidase inhibitor affects influenza infection!
2. Fig-1: Explain how bacterial and viral burden can be quantified!
3. Fig-2: How does the antibody-mediated depletion of NK cells or neutrophils work? What are the targets of the antibody? Why are there less cells after the treatment?
4. Fig-4: The study found that certain genes related to tissue protection and regeneration are specifically downregulated in the context of co-infection. Choose a few genes and explain how they contribute to tissue protection!

Further on disease tolerance

- Miguel Soares, Global Immunotalks
- https://www.youtube.com/watch?v=yTj1e7poPeg