Novel imaging-supported trisomic mouse model of RSV infection for immunological studies of respiratory infections in the context of Down syndrome

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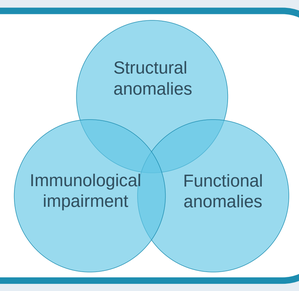
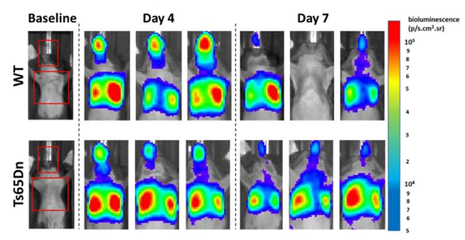
Importance of the study

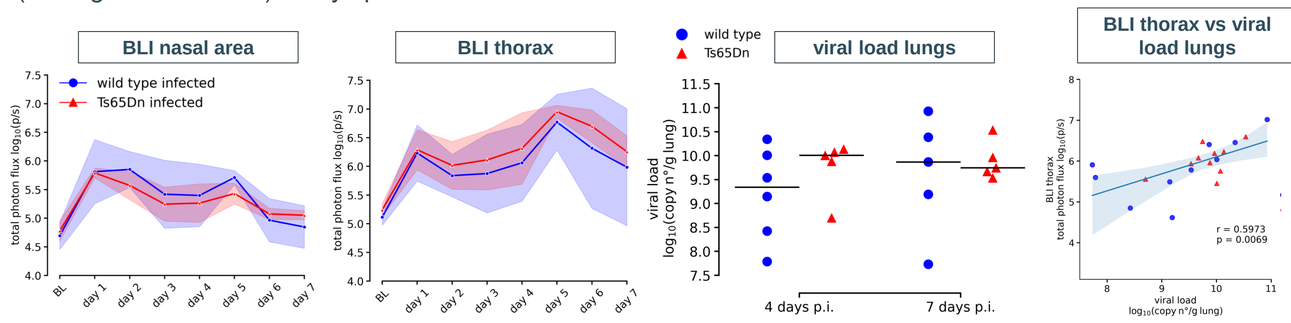
- Individuals with Down syndrome are prone to severe and recurrent lower respiratory tract infections with RSV [1].
- Down syndrome-related structural, functional, and immunological anomalies contribute to infection severity [2].
- We characterized an imaging-based human RSV Ts65Dn Down syndrome mouse model, to longitudinally visualize the infection, pathology, and immune response.



Infection development

- BLI enables **non-invasive spatiotemporal whole-body imaging** of RSV **infection** development.
- Non-invasive **BLI** results **correlated** with invasive **RT-qPCR** results.
- Ts65Dn and wild-type had **similar infection development**.
- **Two wild-type mice** showed **signs of viral clearance on BLI** (BLI signal ≤ baseline) 7 days post-infection.

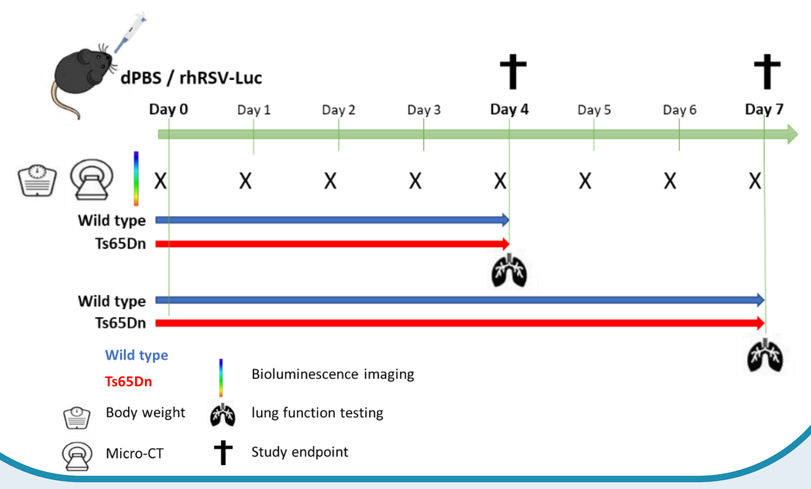




linear-mixed effect model (longitudinal data), Kruskal-Wallis + Man-Whitney post-hoc test with Holm-Bonferroni correction (endpoint data)

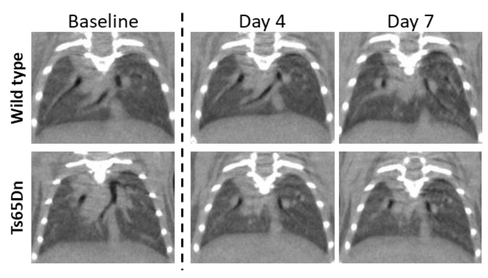
Methodology

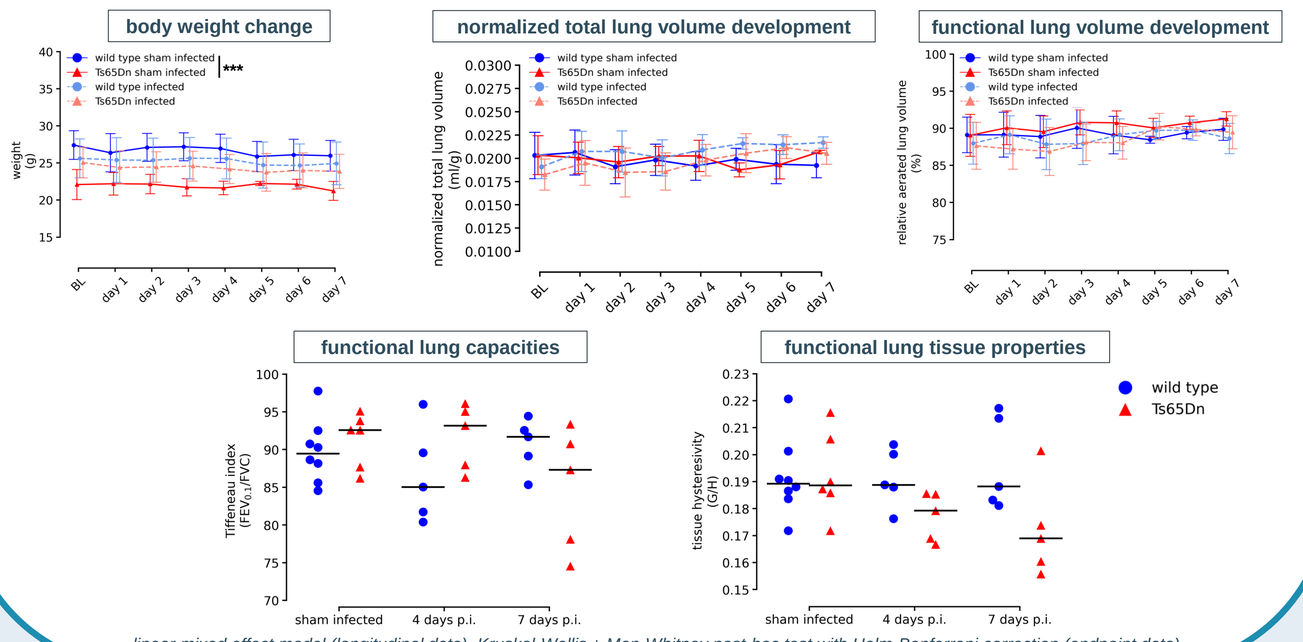
- 5-6 weeks old Ts65Dn mice and euploid littermates
- Intranasally challenged with a **human recombinant RSV luciferase encoding strain** [3]
- Daily **non-invasive imaging** of disease progression
- Infectious development: **bioluminescent imaging** (BLI)
- Pathology development: **micro-computed tomography** (µCT) + **automated delineation** of functional lung volumes (convolutional neural network).
- **Endpoint measurements**: viral load lungs (RT-qPCR), invasive lung function measurement (FlexiVent), bronchioalveolar lavage (BAL) cell count, flow cytometry of the lungs and spleen.



Pathology development

- Infected mice had **no signs of pneumonia**.
- **Functional lung volumes** were **unaffected** during the course of the infection.
- **Lower initial body weight** of sham-infected Ts65Dn mice corresponded with **lower total lung volumes**.
- Non-invasive **µCT results** corresponded with invasive **lung function capacity and tissue property** measurements (Tiffeneau index and tissue hysteresivity).

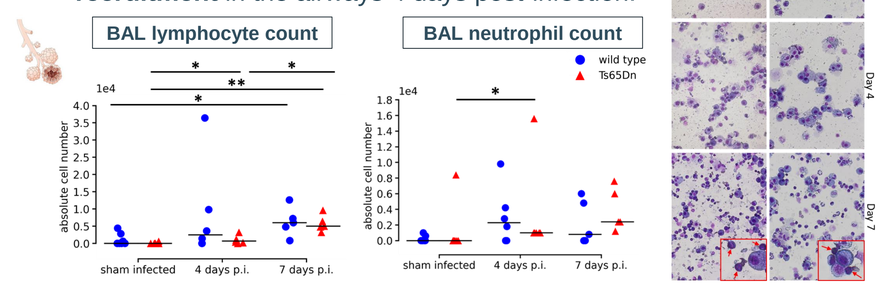




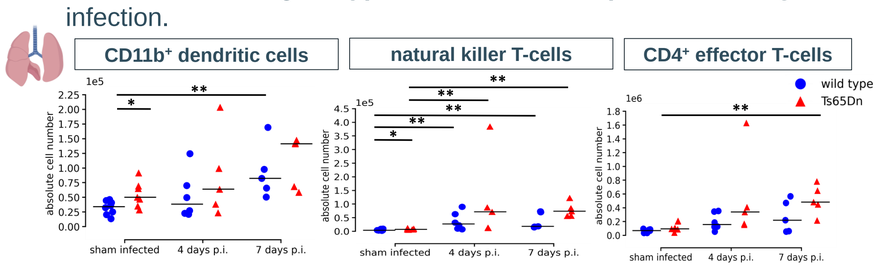
linear-mixed effect model (longitudinal data), Kruskal-Wallis + Man-Whitney post-hoc test with Holm-Bonferroni correction (endpoint data)

Immunological response

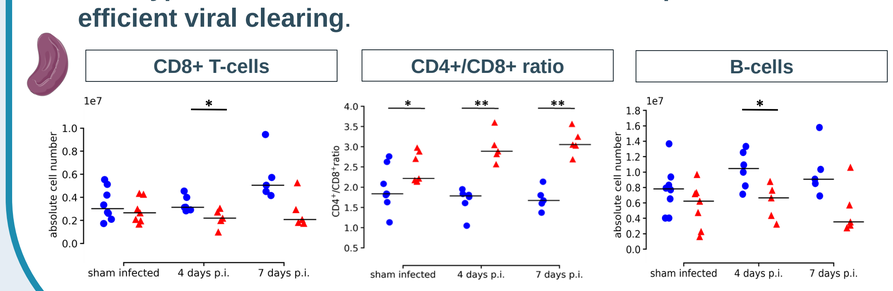
- RSV infection resulted in increased **lymphocyte recruitment in the airways**.
- **Ts65Dn mice** had increased **neutrophil recruitment** in the airways 4 days post-infection.



- **Sham-infected Ts65Dn mice** had increased **pro-inflammatory** CD11b⁺ dendritic cells and natural killer T-cells (NKT) numbers.
- During infection **both genotypes** had upregulated **NKT-cell** numbers and an efficient **CD8⁺ effector T-cell response**.
- An increased CD4⁺ effector T-cell response in **Ts65Dn mice**, suggests a more **extensive genotype-related T-cell response** following infection.



- Absence of myeloid response in the spleen of Ts65Dn mice, suggest a **local myeloid response in Ts65Dn lungs**.
- **Wild-type** mice had **increased B-cell and CD8 T-cell** numbers 4 days post-infection, resulting in genotype related CD4/CD8 T-cell differences.
- **Wild-type** mice had a more **effective humoral response** and a more **efficient viral clearing**.



Kruskal-Wallis + Man-Whitney post-hoc test with Holm-Bonferroni correction (endpoint data); ; *p <0.05, **p <0.01, ***p <0.001, ****p <0.0001

Conclusion

- We reported the **first multimodal-imaging** supported animal model to study lower respiratory tract **infections in the context of Down syndrome.**
- The **Ts65Dn mouse model** showed similar infection and pathology development as wild-type mice with signs of a **less efficient viral clearing and humoral response**.
- Our model has **potential for prophylactic and immunological studies** in the context of lower respiratory tract infections in Down syndrome.

References:

[1] Sánchez-Luna M, Medrano C, Lirio J, the RISK-21 Study Group. Down syndrome as risk factor for respiratory syncytial virus hospitalization: A prospective multicenter epidemiological study. Influenza Other Respi Viruses 2017; 11: 157–164.

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[3] M.-A. Rameix-Welti et al., 'Visualizing the replication of respiratory syncytial virus in cells and in living mice', Nat Commun, vol. 5, no. 1, Art. no. 1, Oct. 2014, doi: 10.1038/ncomms6104.