Characterization of a VSVΔG S (SARS-CoV-2 original variant) hybrid replicating virus as a possible model of mild COVID-19 disease

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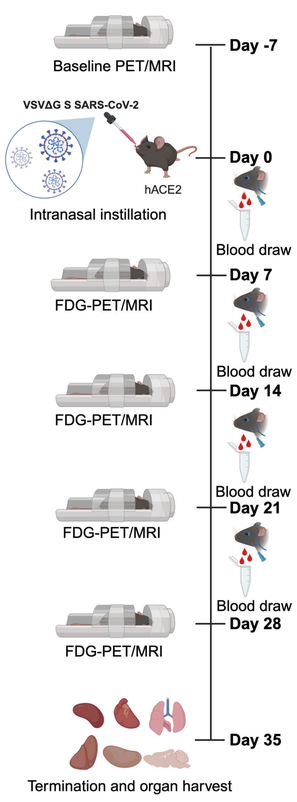
No conflicts of interest.

1 Introduction

- SARS-CoV-2 has led to 776 million infections and ~7 million deaths (Aug 4th, 2024)[1]
- The COVID-19 Immunity Task Force reports a Canadian seroprevalence of infection acquired antibodies of 81.4% as of December 2023
- Post-acute sequalae of COVID-19 (PASC) is estimated to occur in 10% of SARS-CoV-2 cases and has highly variable pathology[2]
- Currently no animal models fully recapitulate PASC[3]
- Molecular imaging can be used to track viral associated inflammation in the body
- Fluoro-2-deoxy-D-glucose (FDG) is preferentially taken up by cells with increased glucose metabolism[4,5]
- COVID-19 is a CL3 pathogen
- `Expensive and difficult to work with
- VSVΔG S expresses the spike protein of COVID-19 to facilitate early research
- ***Goal: Characterize imaging and biological features of infection with a hybrid replicating VSVΔG S (SARS-CoV-2). Compare pathology between variants.***

2 Methods



Mouse model:

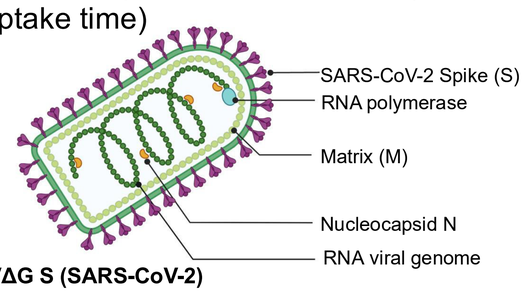
- K-18-hACE2 mice (C57BL/6 background)
- Directed expression to epithelial tissues, mimics human ACE2 distribution

Biological analysis:

- Samples: weekly and terminal blood collection, terminal organ collection
- Flow cytometry for immune phenotyping

FDG-PET/ MRI:

- Sequential MRI and PET scans
- Injection of 500 µCi FDG before MRI (70 mins uptake time)



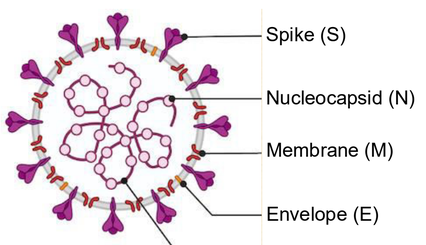
VSVΔG S (SARS-CoV-2)

Groups:

- Low titre: 5X10^4 PFU
- High titre: 1X10^5 PFU
- "Empty" VSVΔG 1X10^6 PFU
- Naïve control

Virus model:

- VSVΔG S SARS-CoV-2 (GFP+)
- Pseudotype virus expressing the S protein of COVID-19 (original variant)
- Intranasal administration to mimic human route of infection



SARS-CoV-2

3 Results

Fig 1.

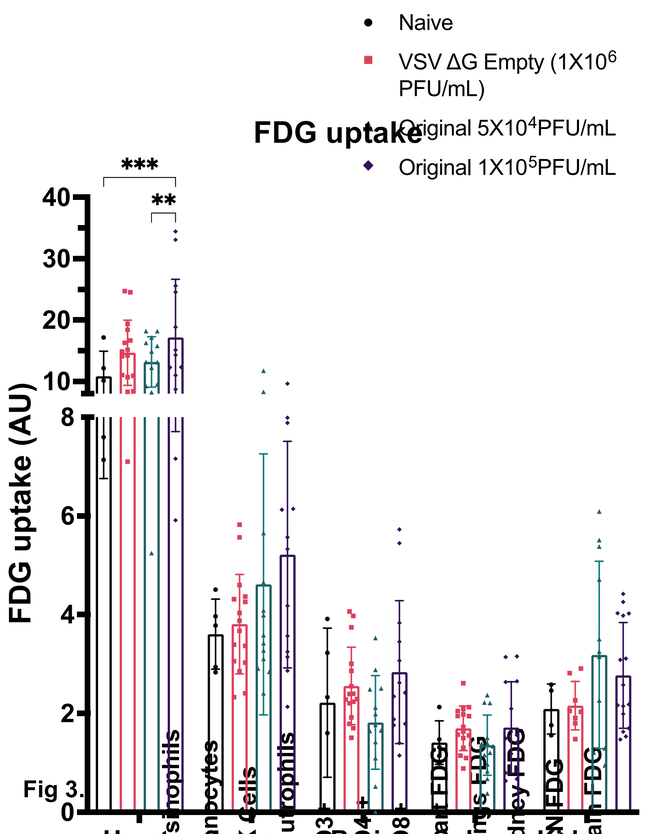
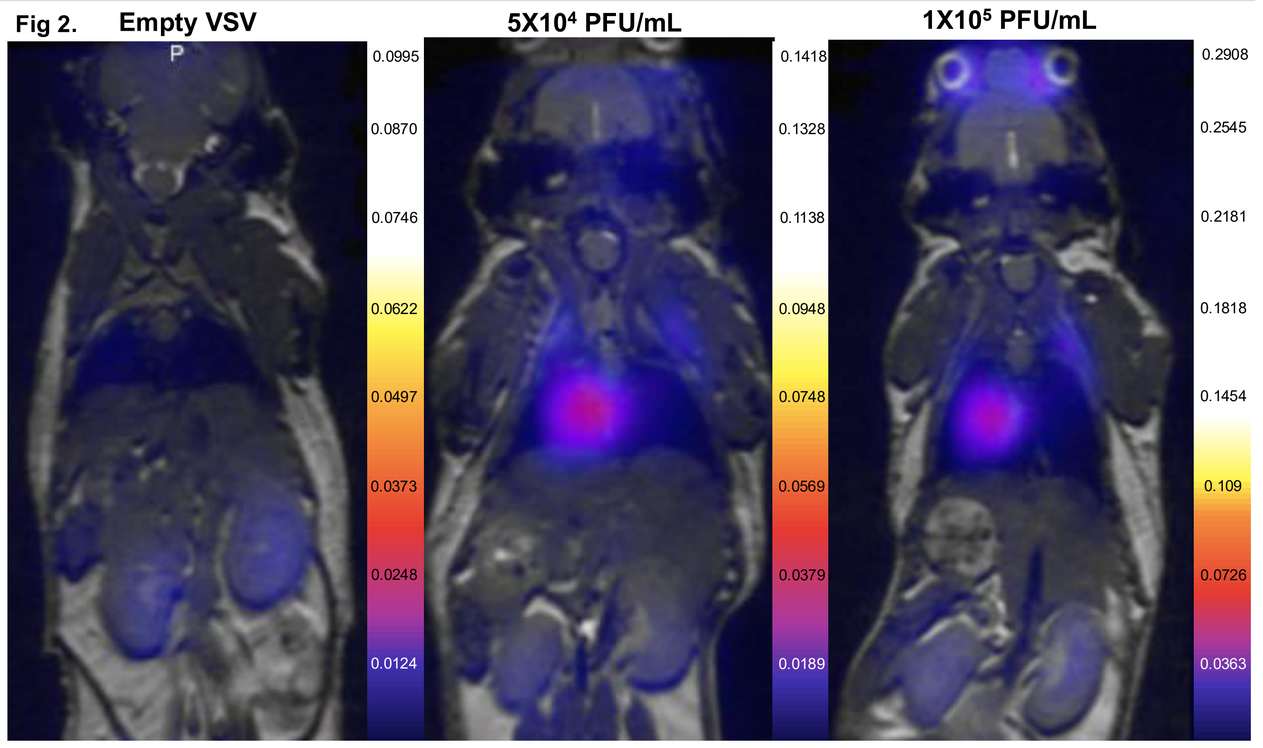


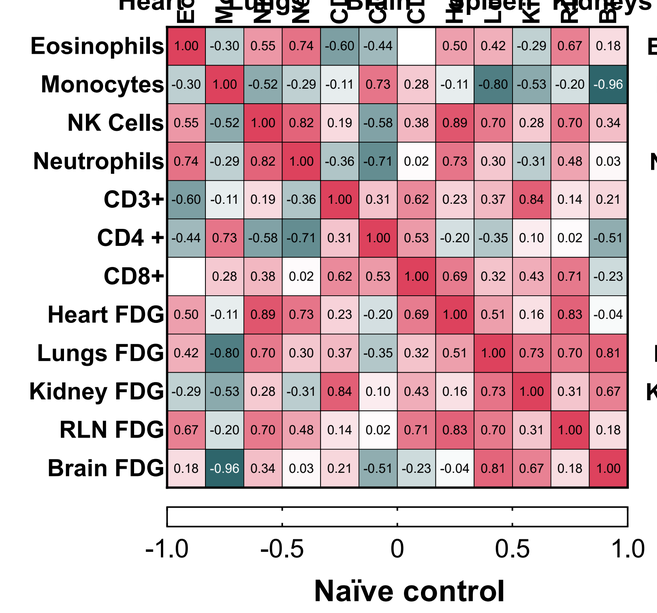
Fig 3.

Figure 1 Normalized FDG uptake values for organs of interest compared between experimental groups. Raw FDG uptake values (MBq/mm^3) for each organ were divided by the FDG uptake values of the muscle in the same scan for internal normalization. Increased FDG uptake in the heart is expected due to its high metabolic requirements. Increased uptake in the lungs was observed for both titres of VSVΔG S SARS-CoV-2 infected groups. Titre-specific FDG increases were observed in the brain and kidneys as well. Overall, the 1x10^5 PFU/mL infected group showed increased FDG uptake compared to other groups ***** P<0.001, ****P<0.0001**

Figure 2 Representative FDG-PET/MRI images from empty VSV 1X10^6 PFU/mL control group, and groups infected with 5X10^4 PFU/mL or 1X10^5 PFU/mL VSVΔG S (SARS-CoV-2 original variant). All images are taken from week 1 of the experimental timeline, with all mice having had appropriate virus instilled intranasally 7 days prior. Colour bars on the side denote the non-normalized FDG concentration in MBq/mm^3. Note that the scale is different for each image due to variations in FDG activity.

Fig 2.





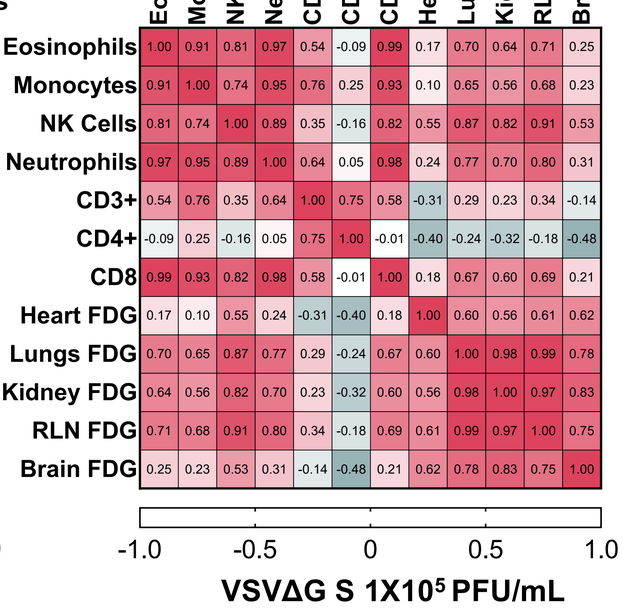


Figure 3 Cell type and FDG uptake correlations are determined by infection type. Pearson correlation matrices of various immune cell types and FDG uptake for naïve control mice and VSVΔG S (SARS-CoV-2 original variant) 1X10^5 PFU/mL infected mice. Immunophenotyping was performed using the BD Celesta flow cytometer.

Fig 4A.

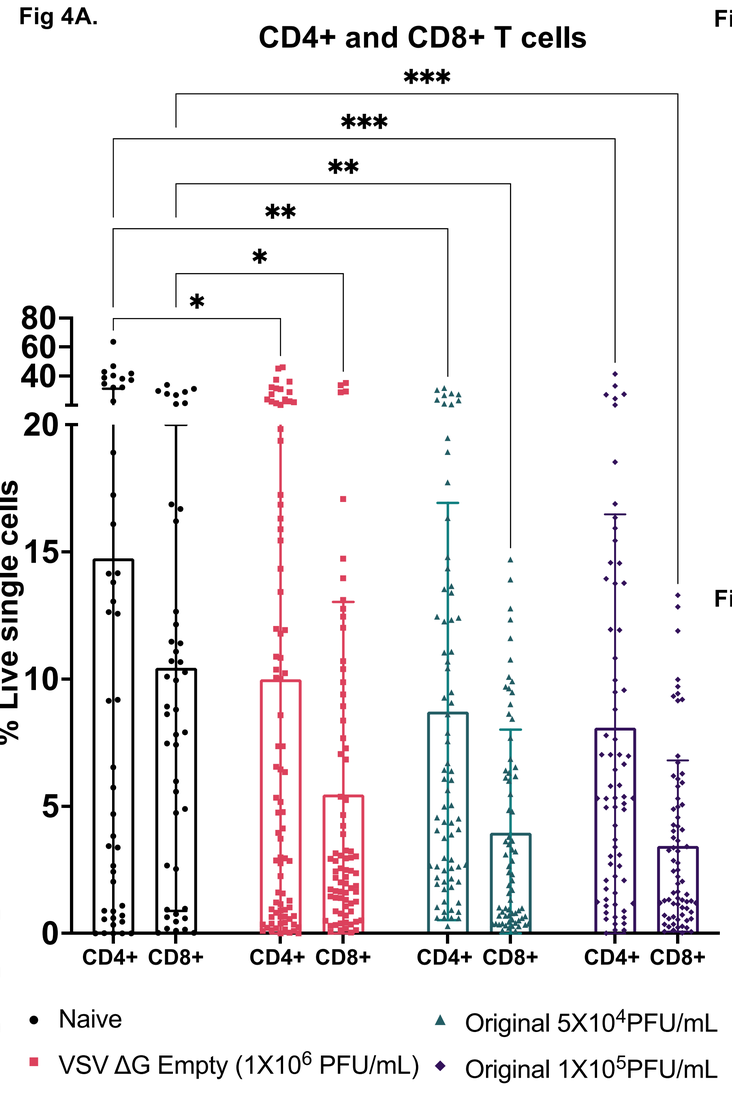


Fig 4B.

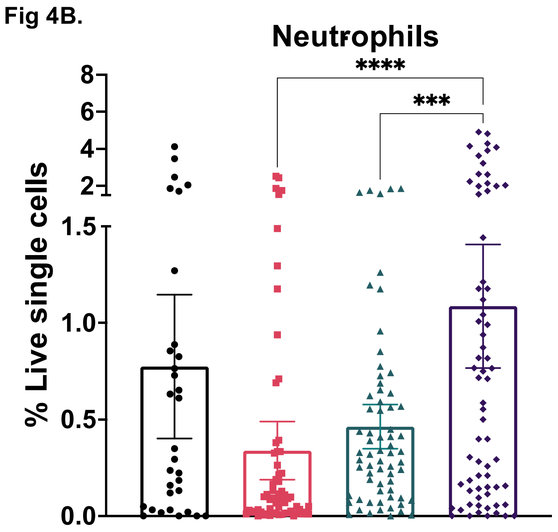


Fig 4C.

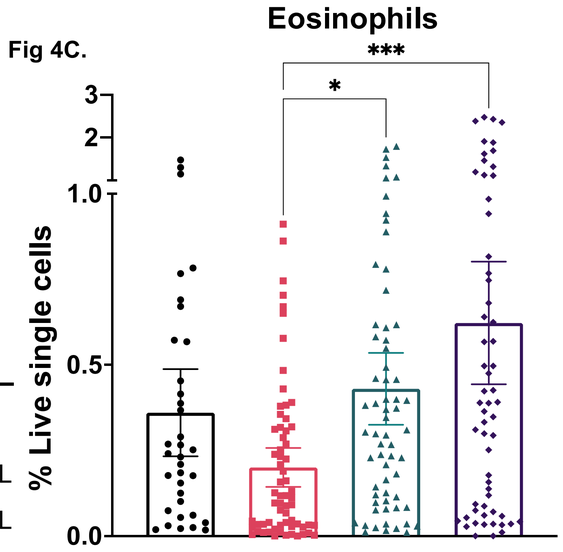


Figure 4 Immune cell changes between experimental groups. A) Comparison of CD4+ and CD8+ T cells between experimental groups. Infected groups showed decreased levels of both cell types when compared to control groups, with cell levels decreasing in a dose-dependant manner. **B)** Comparison of neutrophil (CD11b+, Gr1+) levels between experimental groups. The highest levels were observed in VSVΔG S 1X10^5 PFU/mL, while a slight decrease compared to naïve controls was observed for VSVΔG S 5X10^4 PFU/mL mice. **C)** Comparison of eosinophil (CD11b+, Siglec-F +) levels between experimental groups. Infected groups showed increased cell levels compared to control mice.
*** P>0.5, ** P>0.01, *** P>0.001, **** P>0.0001**

4 Conclusions

- Kidneys and lungs of infected mice showed increased FDG uptake compared to controls
- Infected mice have a correlation in FDG uptake between organs, but this is not the case for uninfected controls
- Infected groups show increased levels of eosinophils, NK cells, and basophils compared to controls
- Infected groups had consistent decreases in CD4+ and CD8+ T cells

5 Future Directions

- Investigate immune differences produced by different SARS-CoV-2 S variants
- Analyze immune phenotypes as a function of time and organ
- Terminate at different points in the study to collect temporal data on organ-level immune populations

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