

# Vitamin D Modulation of Natural Killer Cell Responses to JC Polyomavirus Infection

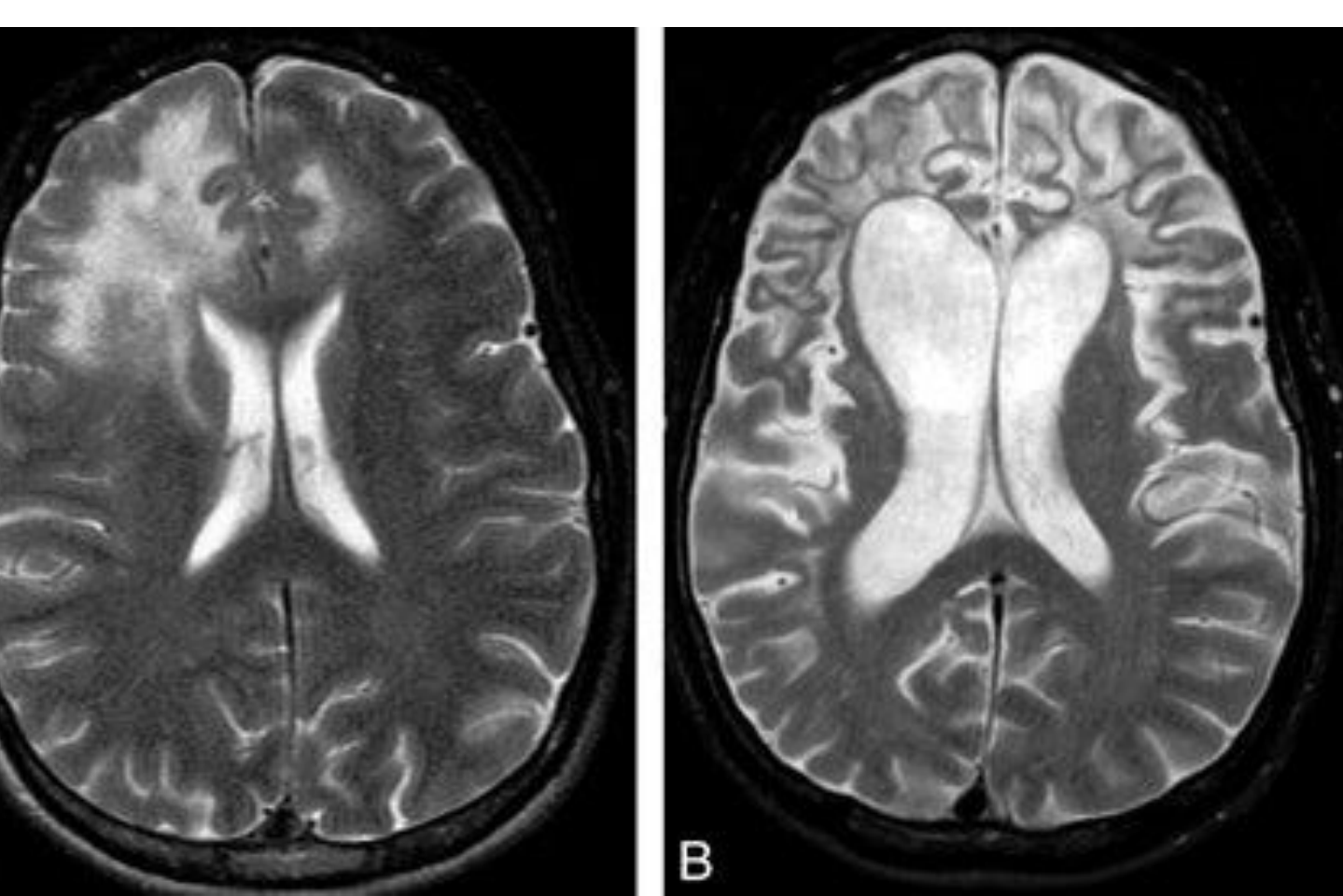
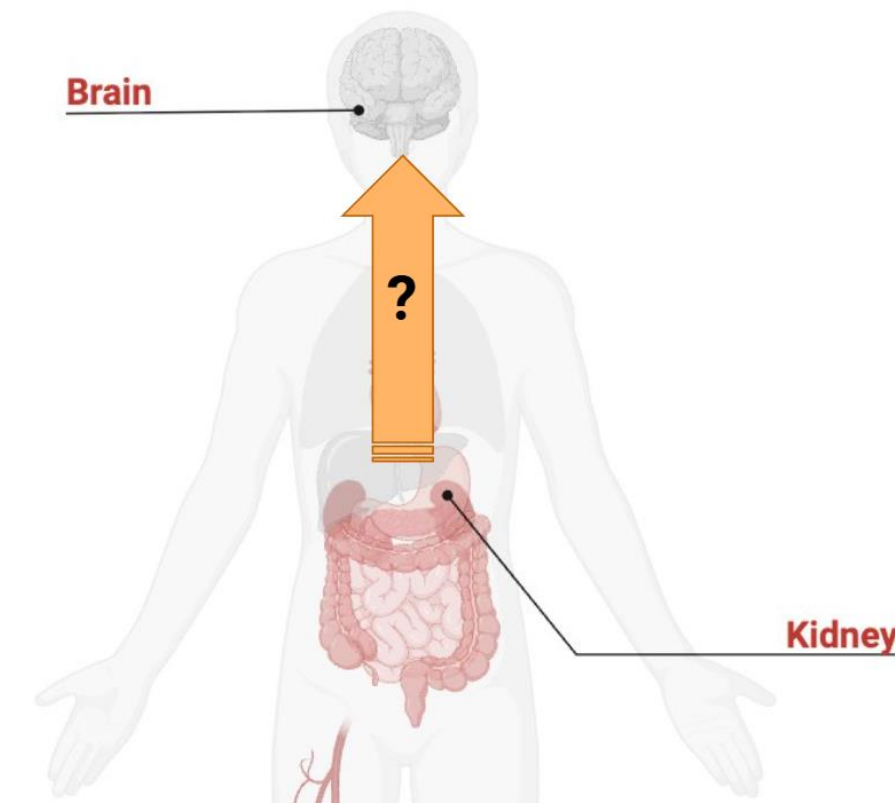
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## Introduction

- JC Polyomavirus (JCPyV) is a circular double-stranded DNA virus that causes benign infection and viral replication in the kidney tubules.
- It can only infect humans, with a seroprevalence of ~60-80% in the healthy population.
- Severe immunosuppression may lead to JCPyV reactivation, which causes JC to exit the kidney and enter the brain.
- Reactivation of JCPyV leads to progressive multifocal leukoencephalopathy (PML); an often fatal, demyelinating disease of the brain.



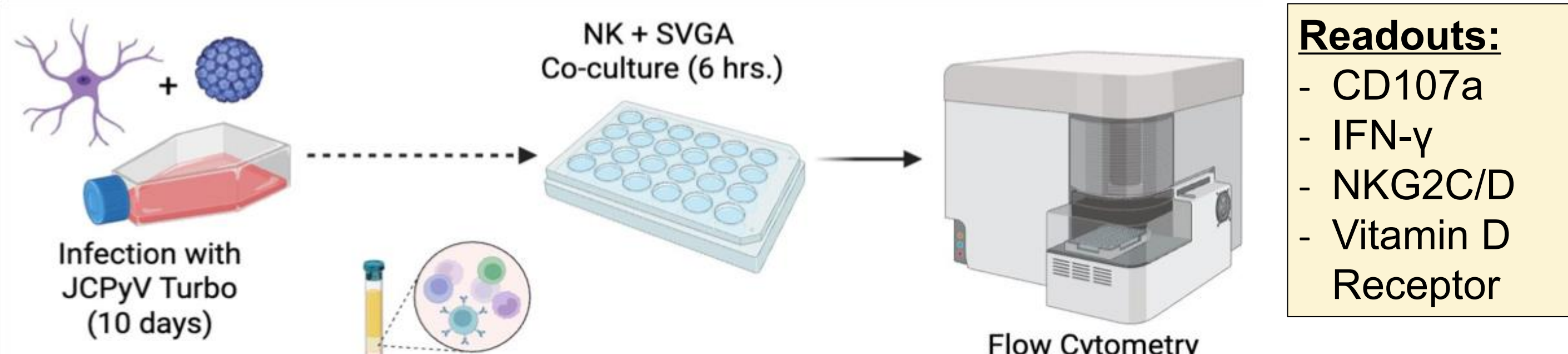
- After PML diagnosis, there is about a 30-50% mortality within the first few months.
- Currently, no treatment for PML.

- Studies in renal transplant recipients showed that vitamin D deficiency may increase BK polyomavirus burden; but the role of vitamin D in JCPyV infection remains unexplored.
- Vitamin D could exert immunomodulatory effects on immune cells, including human natural killer (NK) cells.
- NK cell cytotoxicity is key to controlling JCPyV.

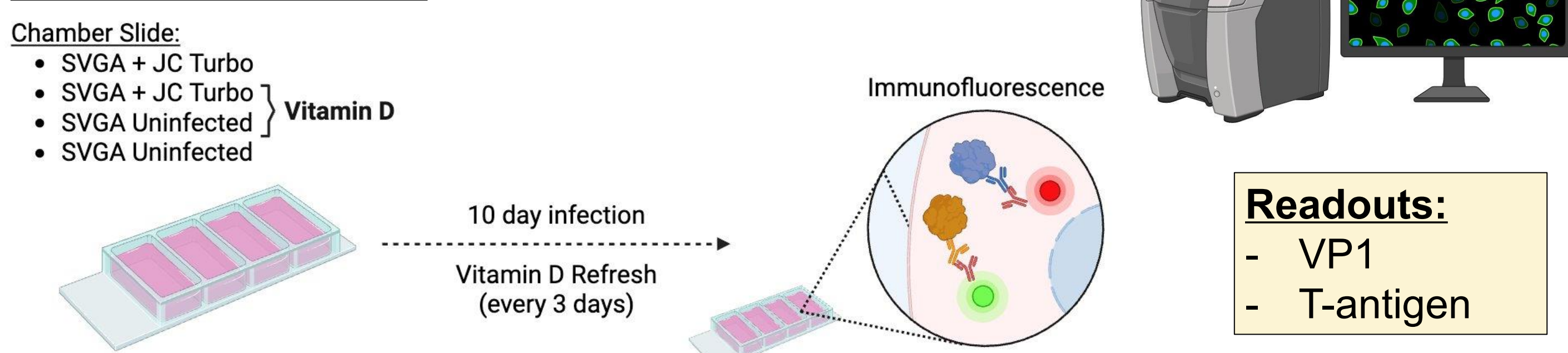
## Hypothesis and Methods

Vitamin D, also known as calcitriol, will improve NK cell function in response to JCPyV infection, as well as decrease direct infection of susceptible cell types.

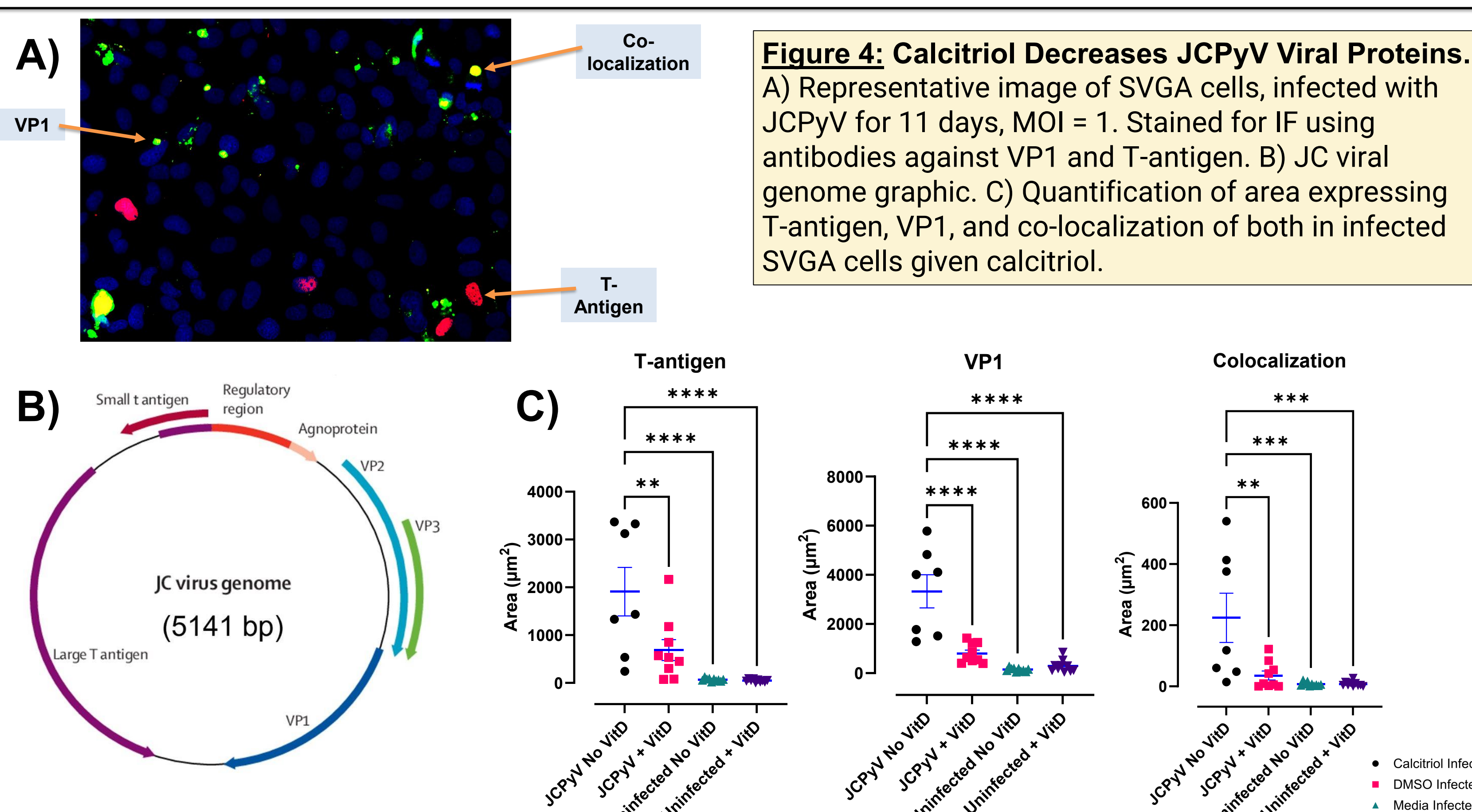
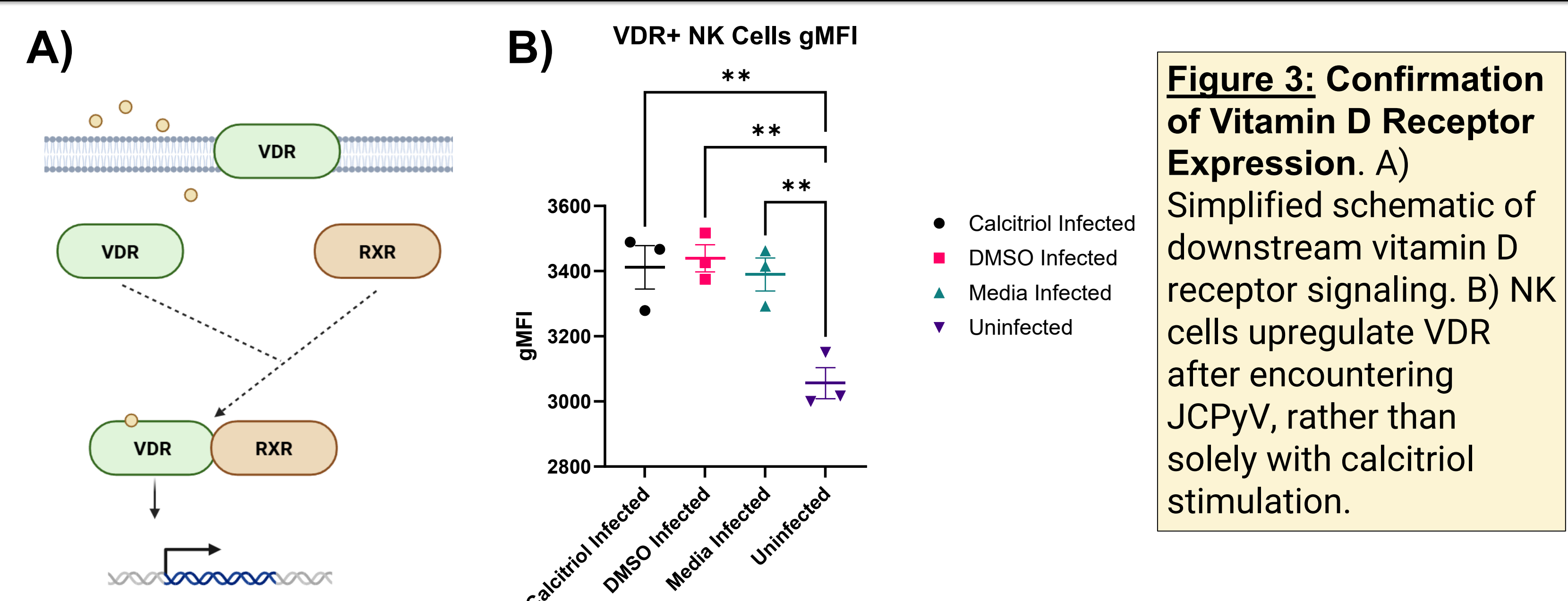
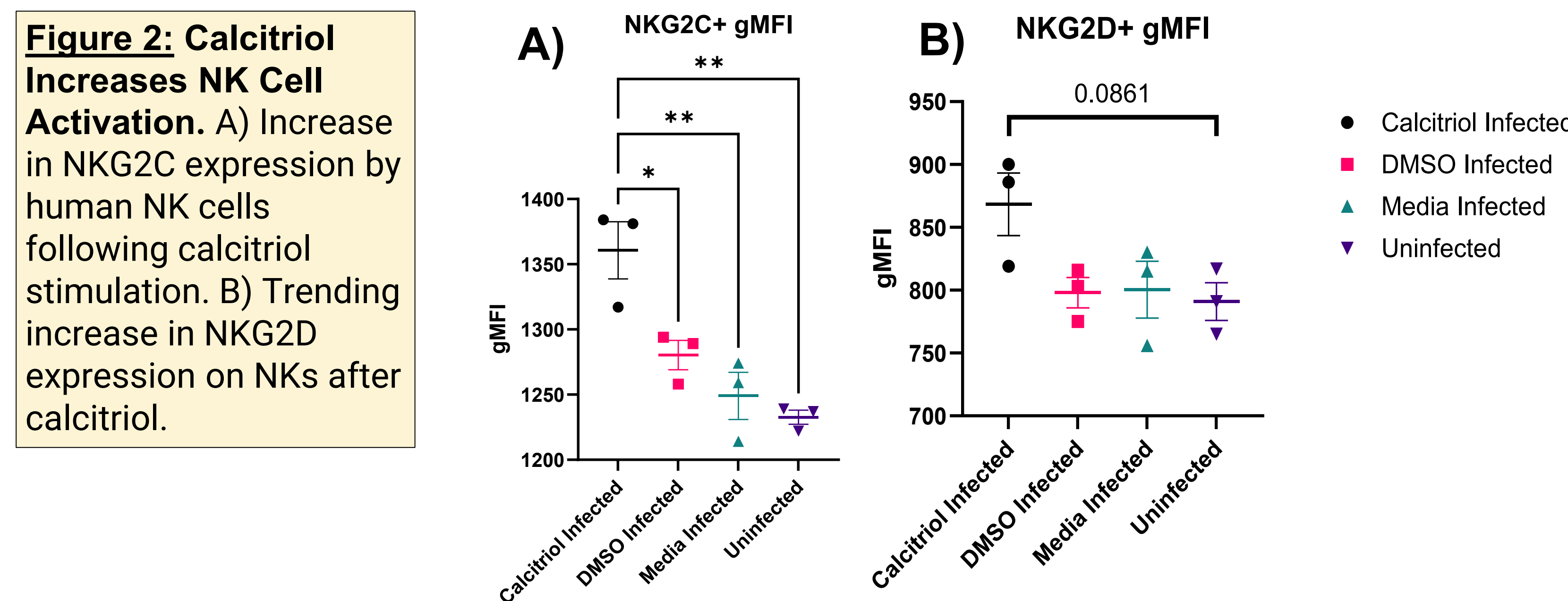
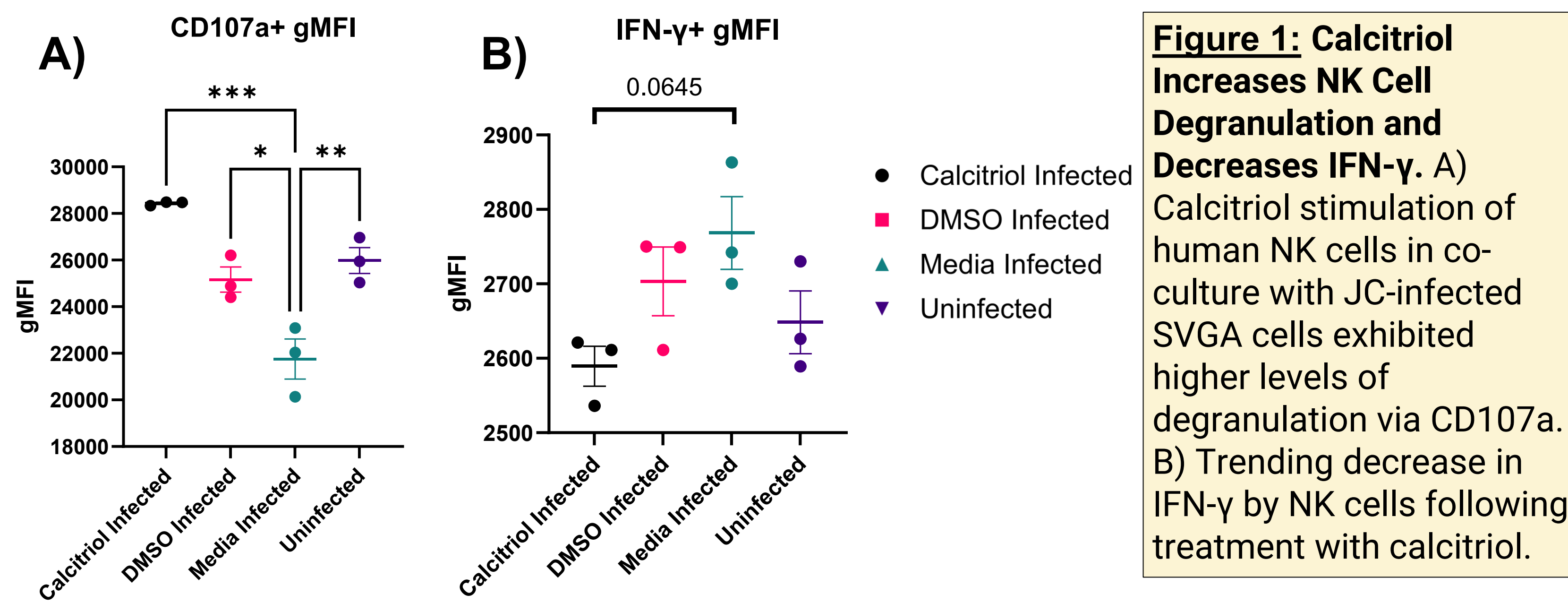
### Flow Cytometry



### Immunofluorescence



## Results



## Conclusions

- Calcitriol supplementation bolsters NK cell functionality in response to JCPyV via increased CD107a
- NK cells also exhibit increased activation following calcitriol treatment, shown by higher NKG2C and NKG2D
- Human NK cells upregulate VDR in response to JCPyV
- Treating target cells of JCPyV infection directly with calcitriol decreased viral proteins, VP1 and T-antigen

## Future Directions

- Further profile human NK cells following calcitriol treatment
  - NKG2A, perforin, granzyme, and exhaustion marker expression
- Investigate effects of calcitriol downstream of the vitamin D receptor
- Treat other JCPyV susceptible cell types with calcitriol to assess ability to decrease overall infection
  - Primary astrocytes, oligodendrocytes, and kidney epithelium

## References

- Weeres MA, Robien K, Ahn YO, Neulen ML, Bergerson R, Miller JS, Verneris MR. The effects of 1,25-dihydroxyvitamin D3 on in vitro human NK cell development from hematopoietic stem cells. *J Immunol.* 2014 Oct 1;193(7):3456-62. doi: 10.4049/jimmunol.1400698. Epub 2014 Aug 22. PMID: 25149465; PMCID: PMC4363084.
- Ota K, Dambaeva S, Kim MW, Han AR, Fukui A, Gilman-Sachs A, Beaman K, Kwak-Kim J. 1,25-Dihydroxy-vitamin D3 regulates NK-cell cytotoxicity, cytokine secretion, and degranulation in women with recurrent pregnancy losses. *Eur J Immunol.* 2015 Nov;45(11):3188-99. doi: 10.1002/eji.201545541. Epub 2015 Sep 7. PMID: 26257123.

## Acknowledgements

- Tan Lab and all lab members
- Iowa Inflammation Program
- University of Iowa Flow Cytometry Core
  - Health Vignes
- Iowa Immunology Graduate Program

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