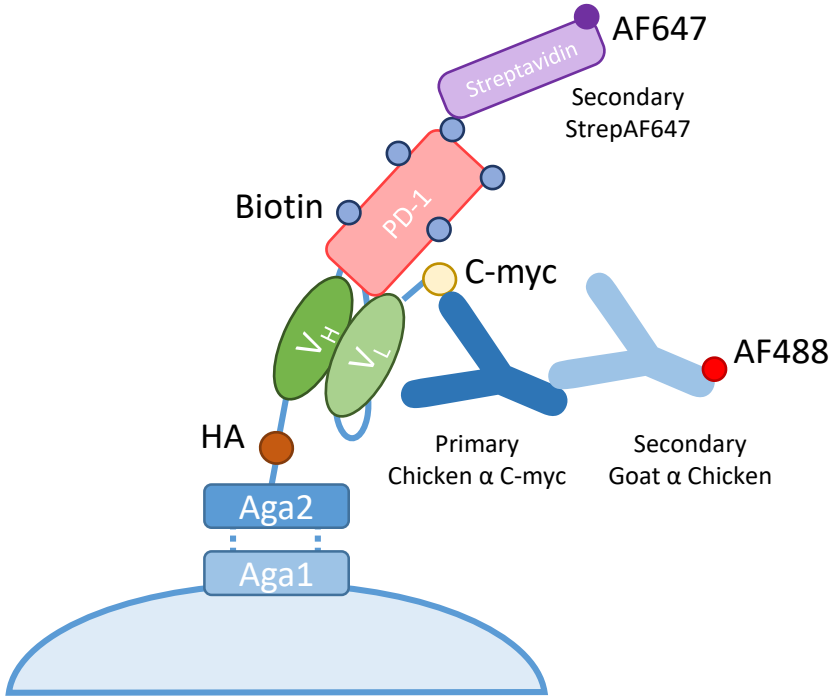
20.109 Guest Lecture

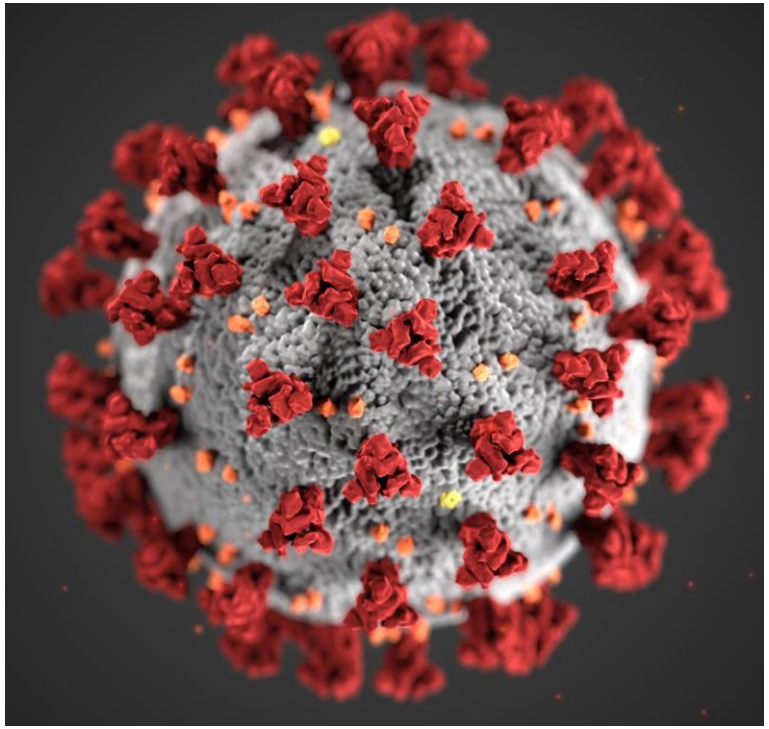
Sarah Cowles

April 23, 2020

Effect of affinity on anti-PD-1 immune checkpoint blockade therapy



Spotlight on MIT COVID-19 work: Vaccine, Drug, and Testing Development



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Immune Checkpoint Blockade Therapy

In the Wittrup lab, we uses a variety of protein engineering strategies to understand and develop effective cancer biopharmaceuticals…

Dr. James P. Allison Dr. Tasuku Honjo

2018 Nobel Prize in Physiology or Medicine for the discovery of cancer therapy by inhibition of negative immune regulation

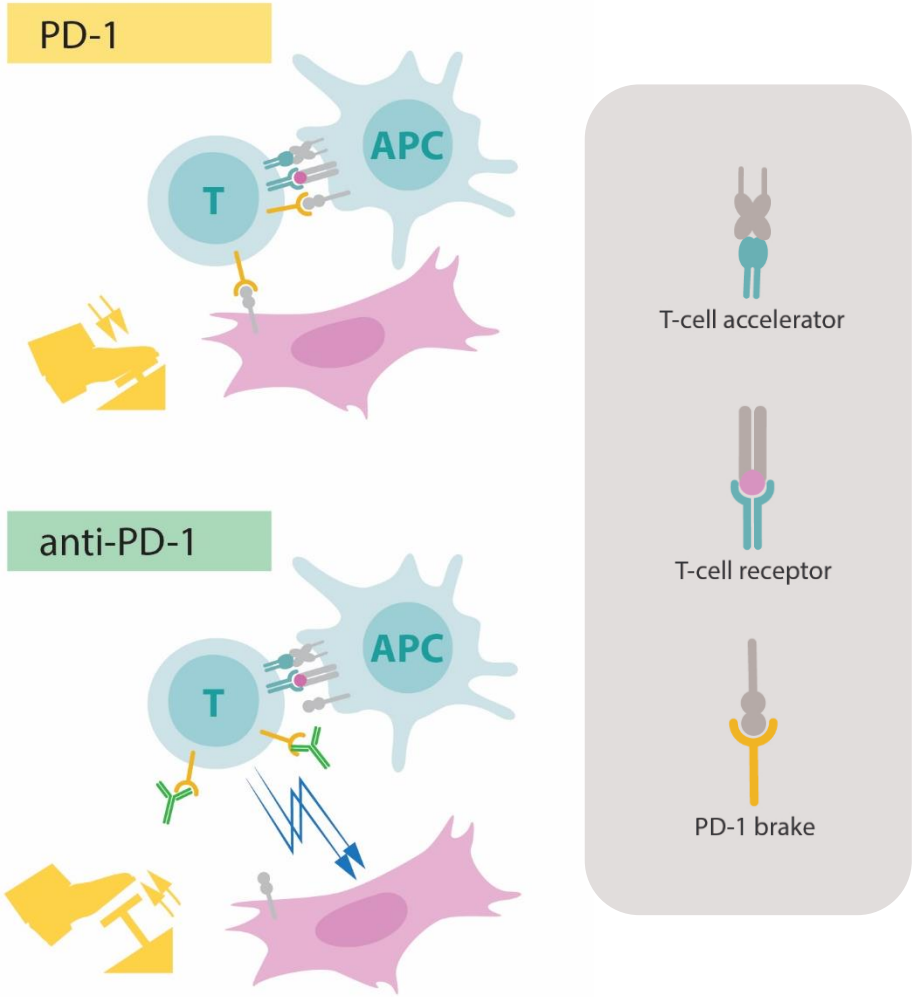
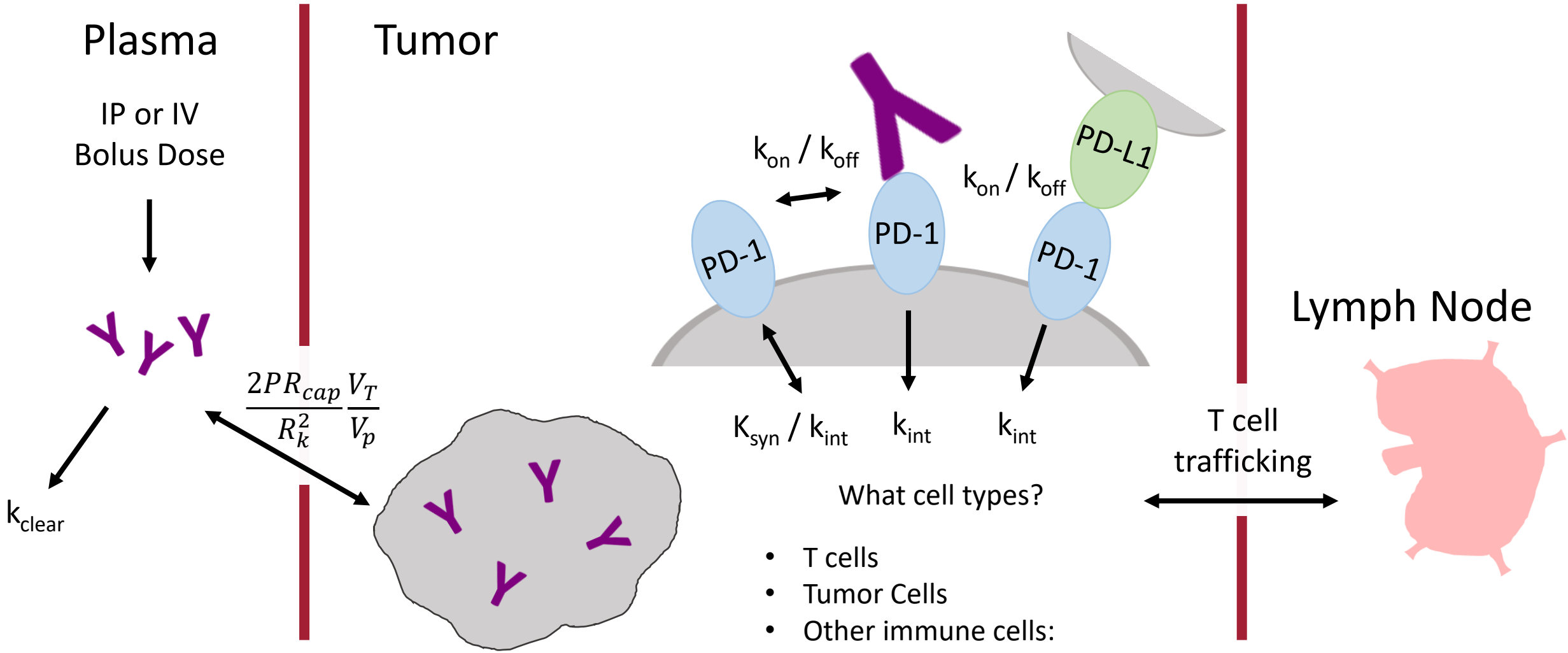


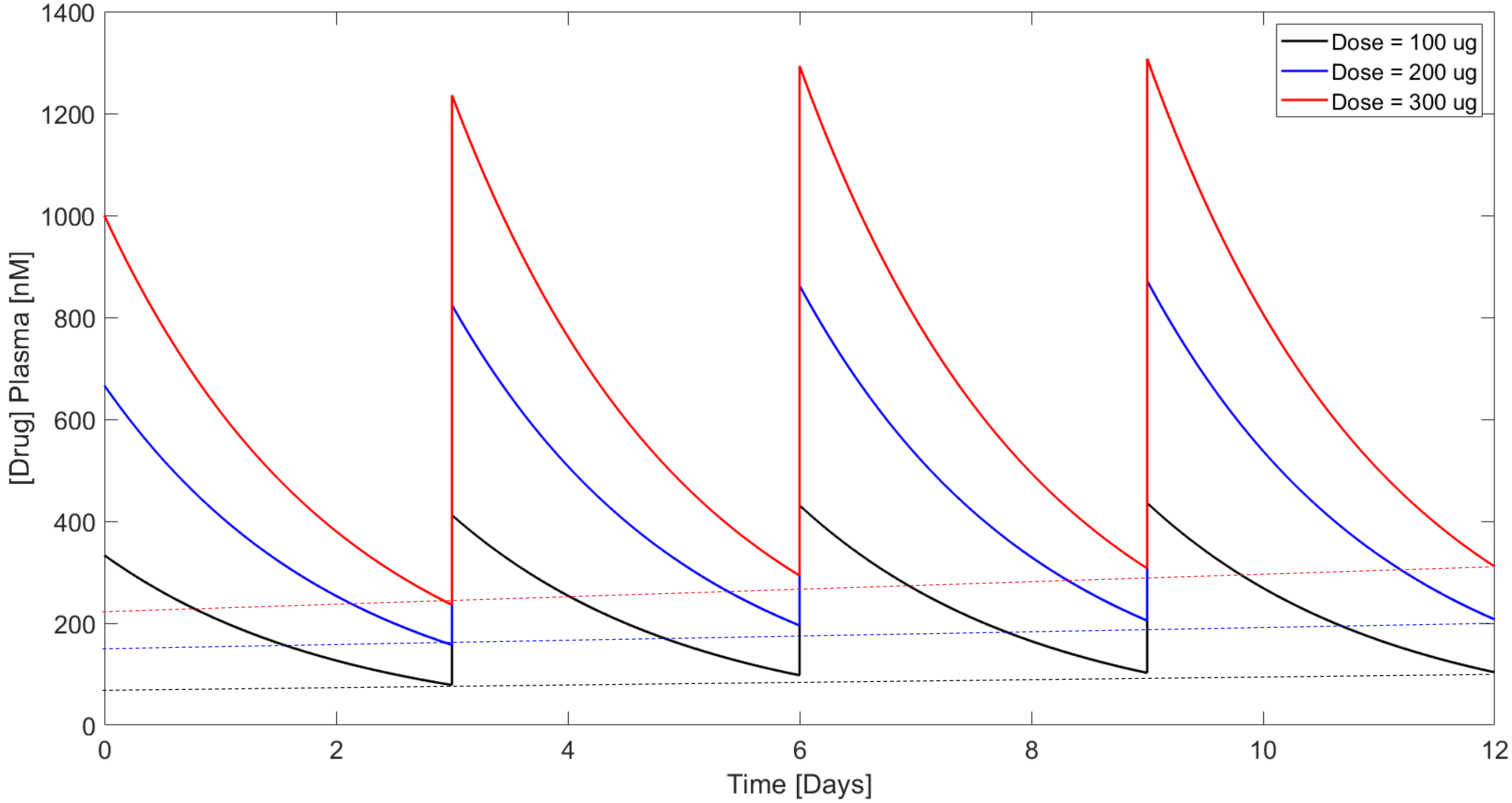
Illustration by Mattias Karlen, The Nobel Committee for Physiology or Medicine

https://www.nobelprize.org/uploads/2018/10/press-medicine2018.pdf

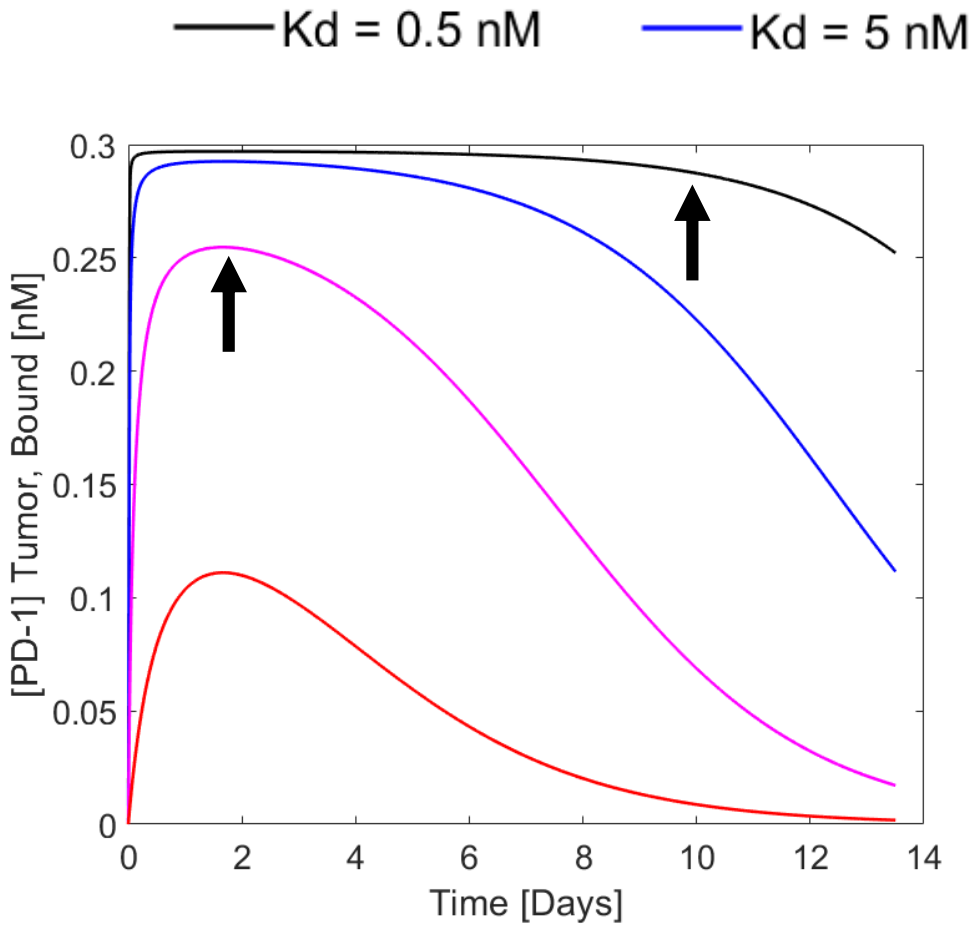
Moving to a PD-1 specific model

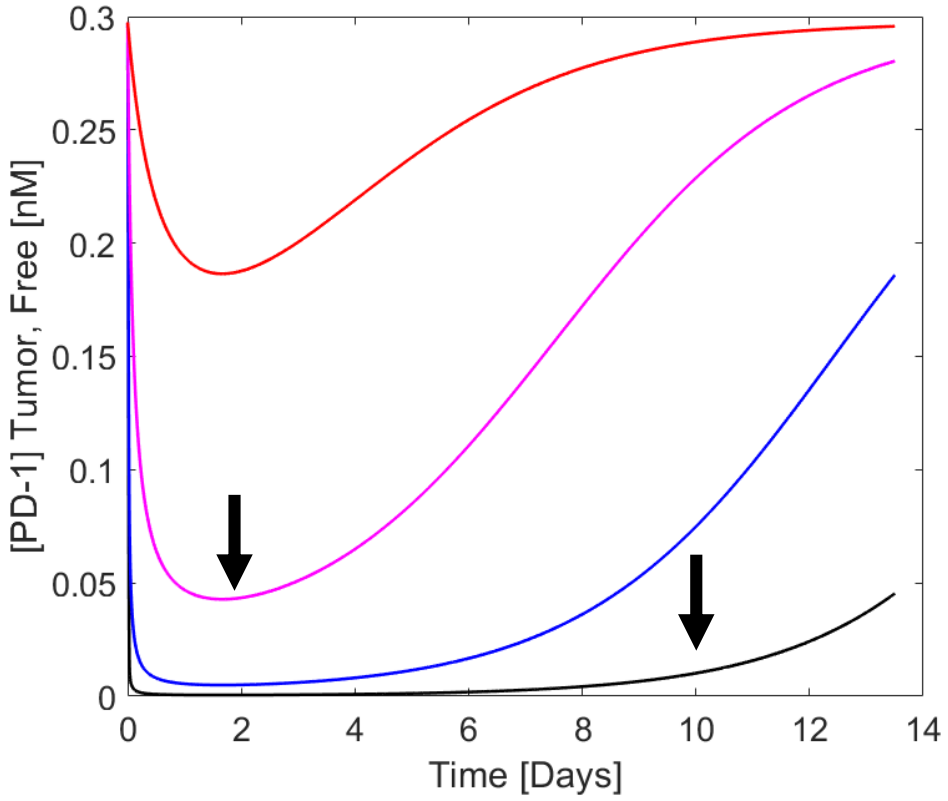


Modeling the concentration of drug in plasma

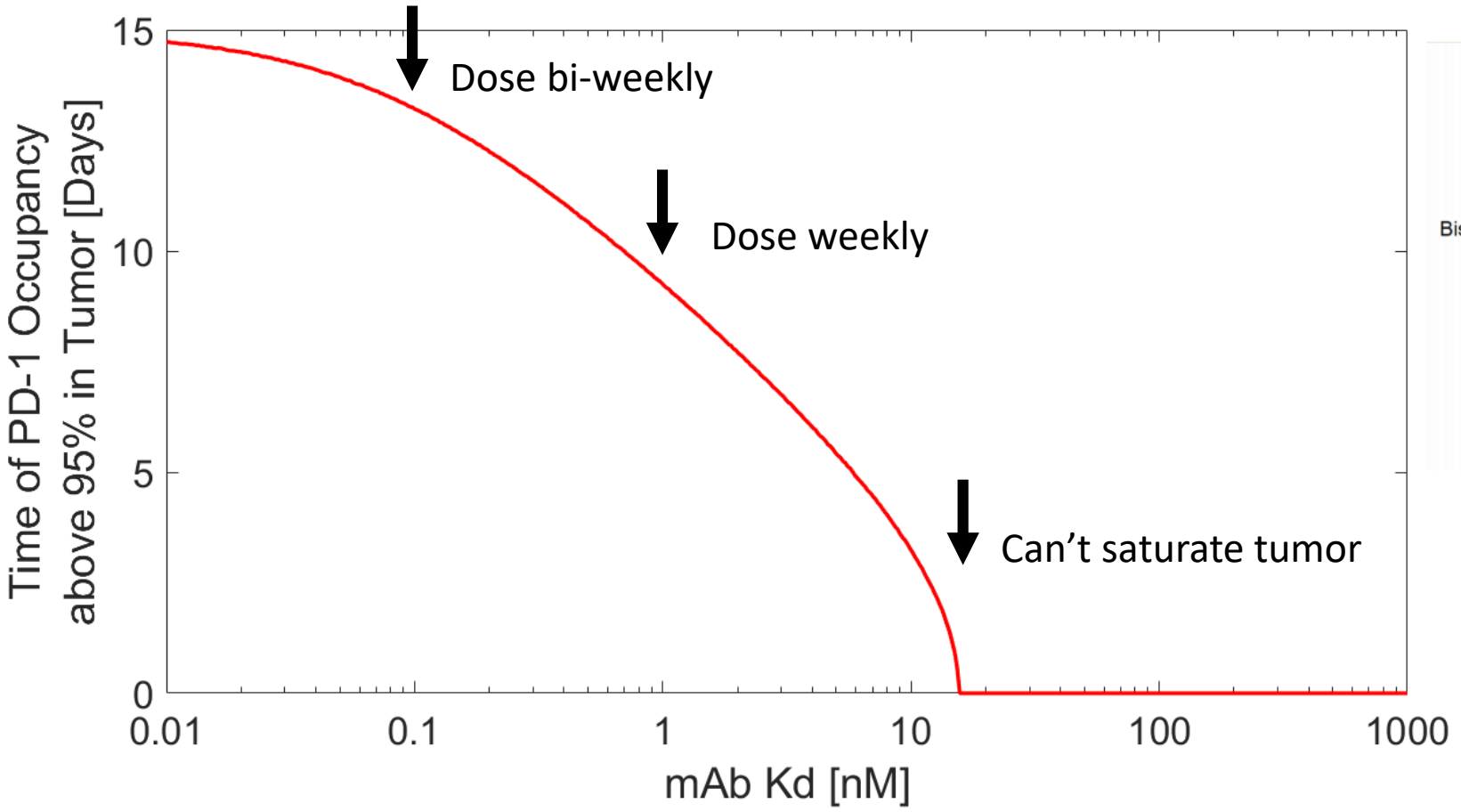


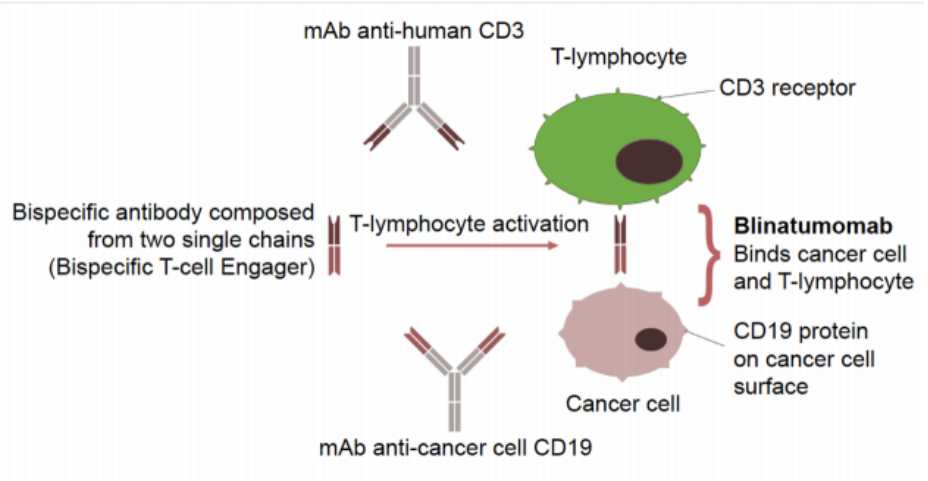
Modeling the receptor occupancy in the tumor





How long does drug stay bound to PD-1 in tumor?





Blinatumomab $t_{1/2}$ = ~2 hours !
Requires continuous IV administration

Anti-PD-1 $t_{1/2}$ = ~35 hours (mice)
Anti-PD-1 $t_{1/2}$ = ~27 days (humans)

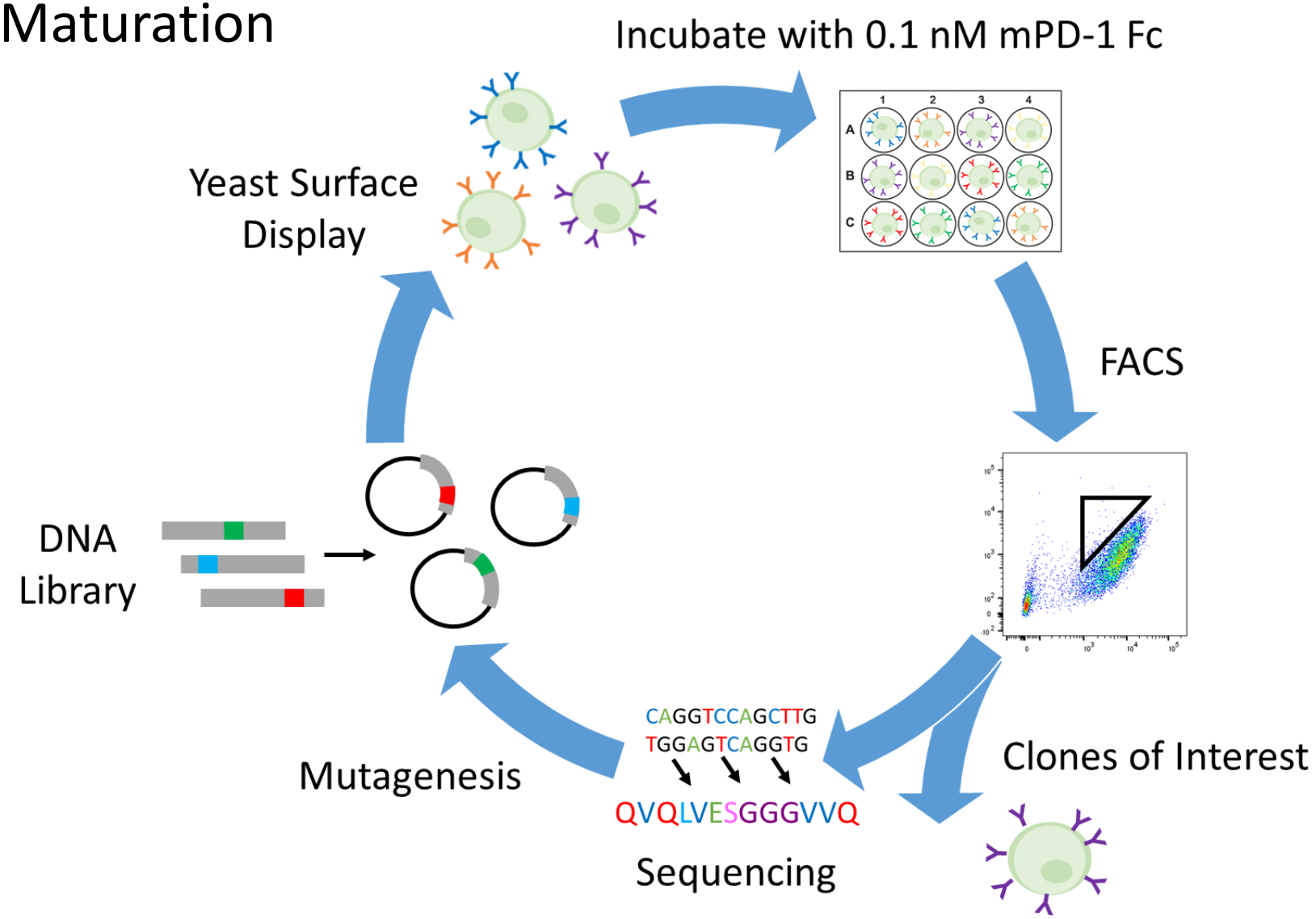
Can we replicate this in vivo?

We need to make a set of anti-PD-1 antibodies with varying affinities

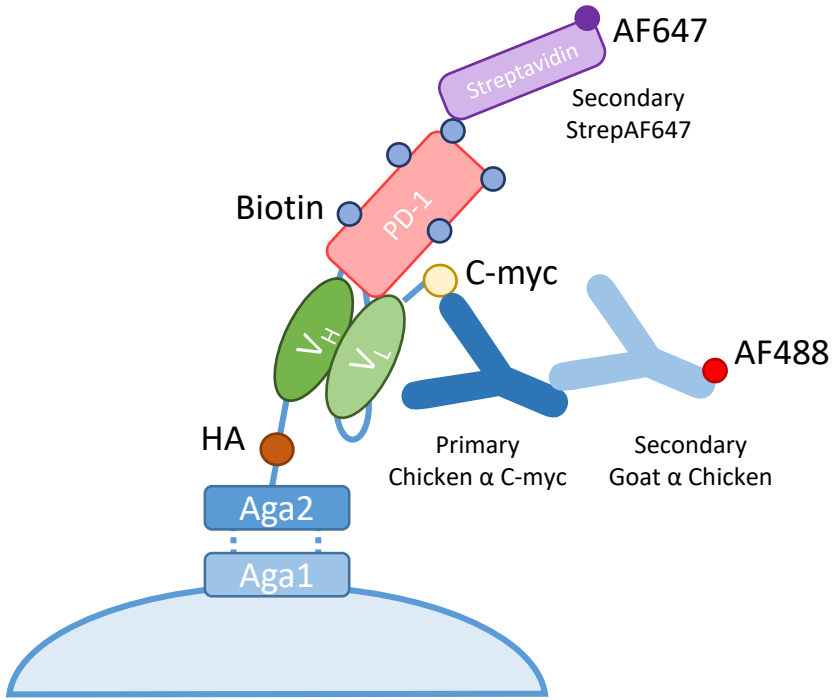
Zhu, M., Wu, B., Brandl, C. *et al., Clin Pharmacokinet* **55,** 1271–1288 (2016).

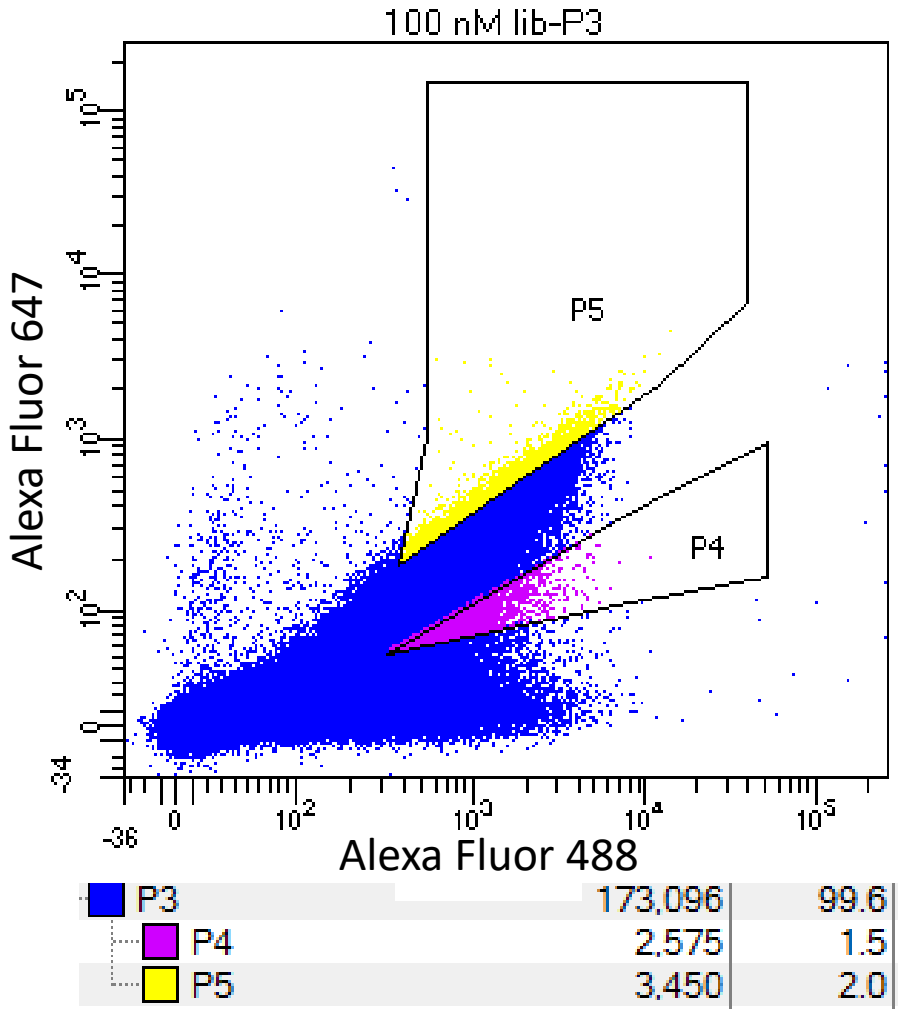
How do we change the binding affinity of anti-PD-1?

Affinity Maturation



Anti-PD-1 scFv Library





P3	173,096	99.6
P4	2,575	1.5
P5	3,450	2.0

Anti-PD-1 Mutants

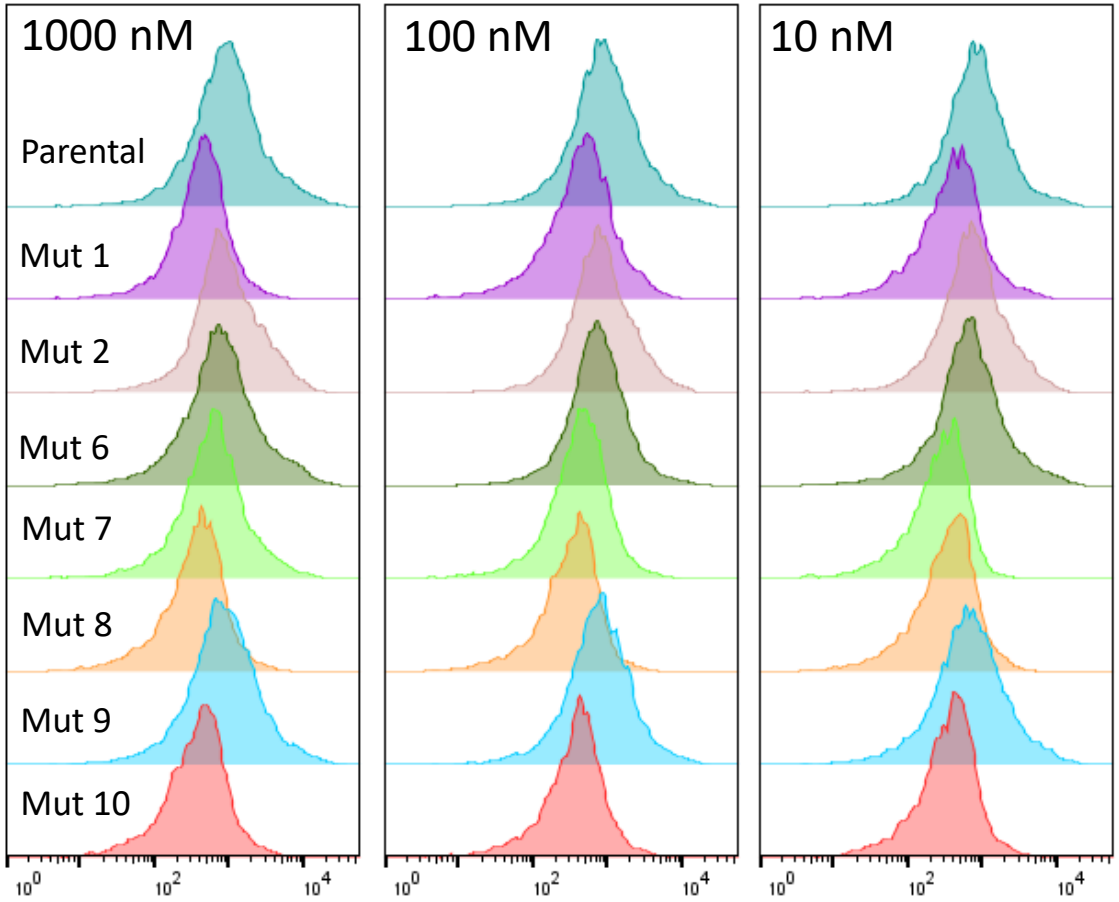
Heavy Chain Mutants

	CDR H1	CDR H2	CDR H3
	QVQLQQSGAELVKPGSSVKISCKASGYTFTSHFIHWIKQQPGNGLEWIGGIYPGDGDTEYNQQFNGKATLTADKSSSTAYMRLSSLTSEDSAVYFCATRVPSYWFFDFWGPGTMVTVSS		
Mut1 F95L			L
Mut2 Y60H		H	
Mut6 S25A	A		
Mut7 K23E S102P	E		P
Mut8 S16T Y80H S91A	T	H	A
Mut9 F105S			S

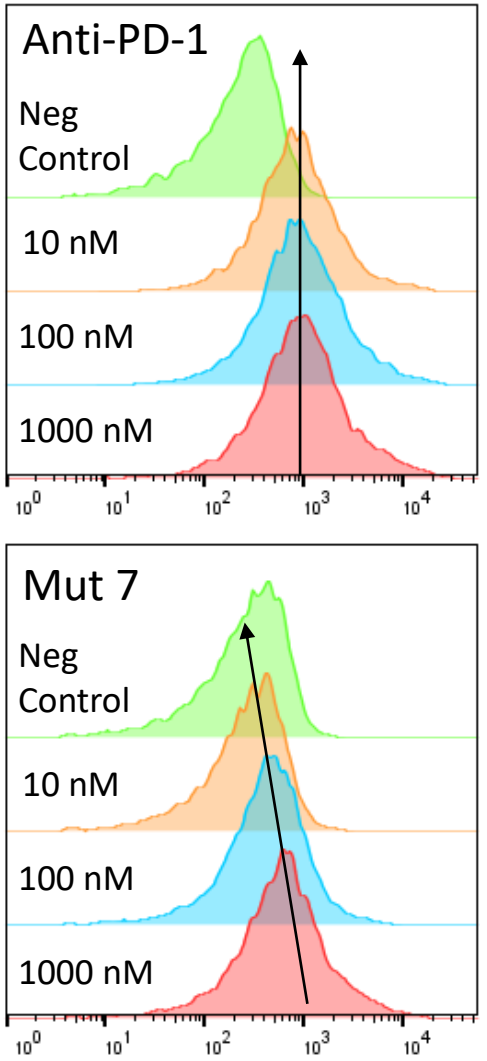
Light Chain Mutants

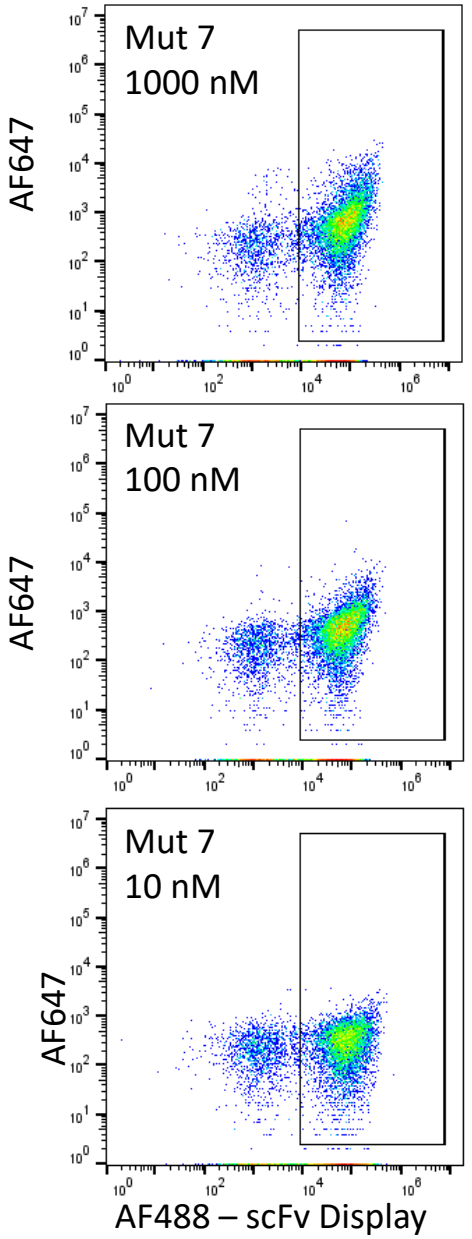
	CDR L1	CDR L2	CDR L3
	DVALTQTPVAQPVTLGDQASISCRSSQSLVHSNGRTYLEWYLQKPGQSPQLLIYKVSNRFSGVPDRFIGSGSGSDFTLTISRVEPEDLGVYYCFQATHDPNTFGAGTKLELK		
Mut10 G16E	E		

Anti-PD-1 mutant low affinity clones

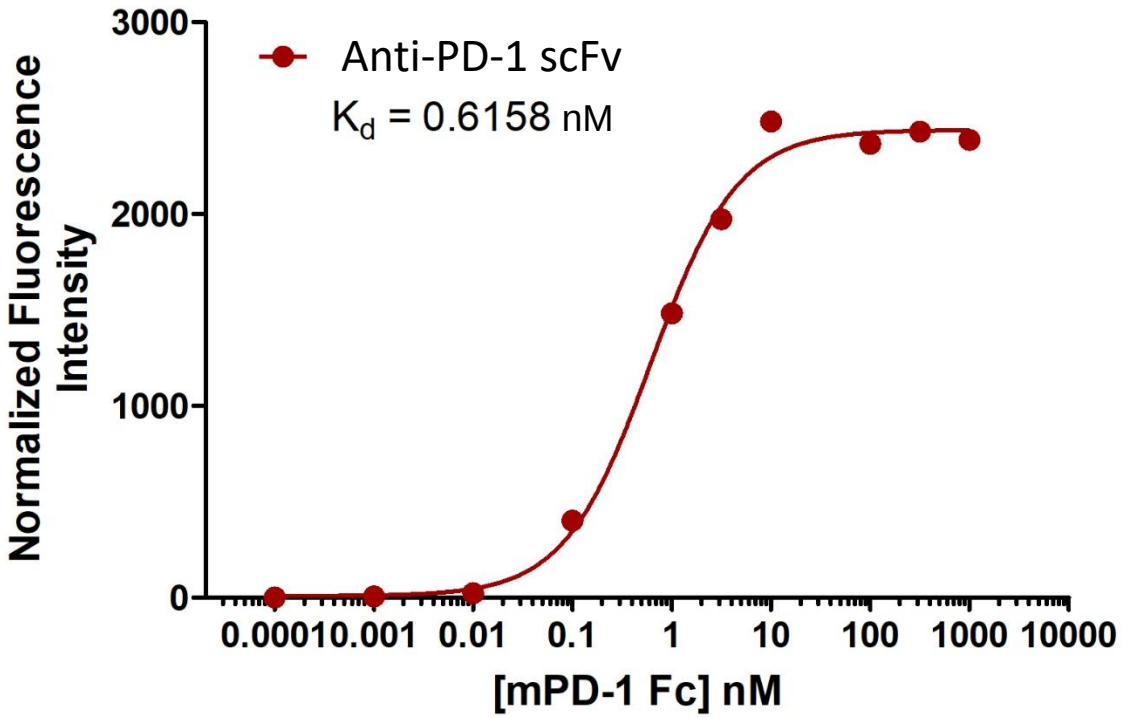


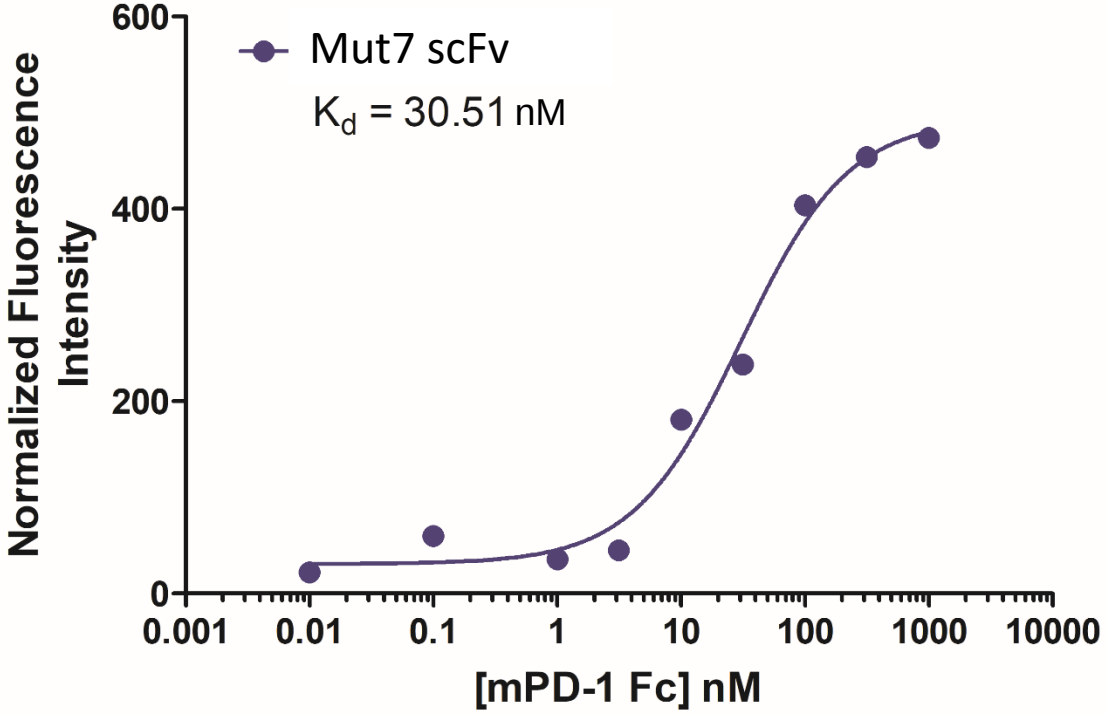
Alexa Fluor 647 Signal = Anti-PD-1 Binding





Anti-PD-1 and Mutant 7 Titration mPD-1

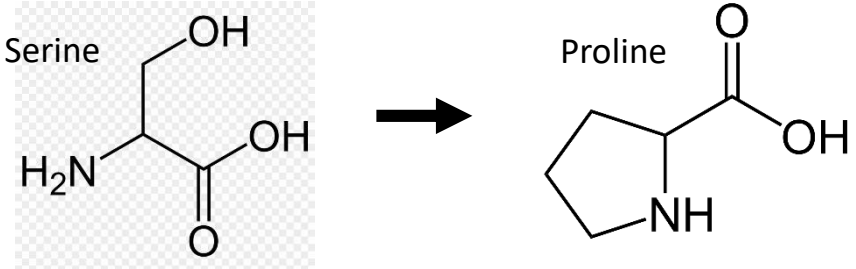




CDR H1 **CDR H2** **CDR H3**

QVQLQQSGAELVKPGSSVKISCKASGYTFTSHFIHWIKQQPGNGLEWIGGIYPGDGDTEYNQQFNGKATLTADKSSSTAYMRLSSLTSEDSAVYFCATRVPSYWFFDFWGPGTMVTVSS

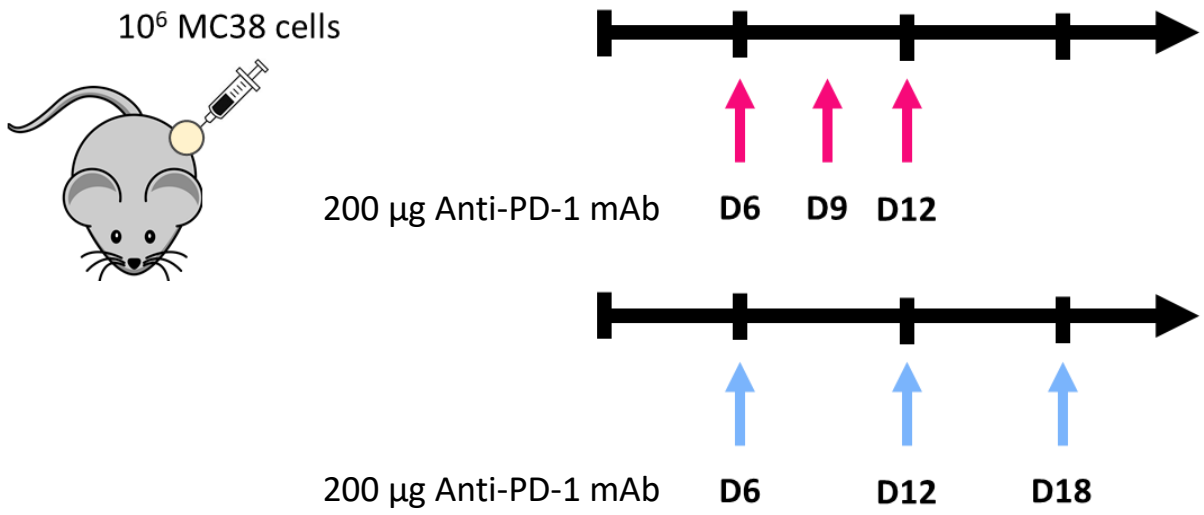
Mut7 K23E S102P ····· E ····· P ·····

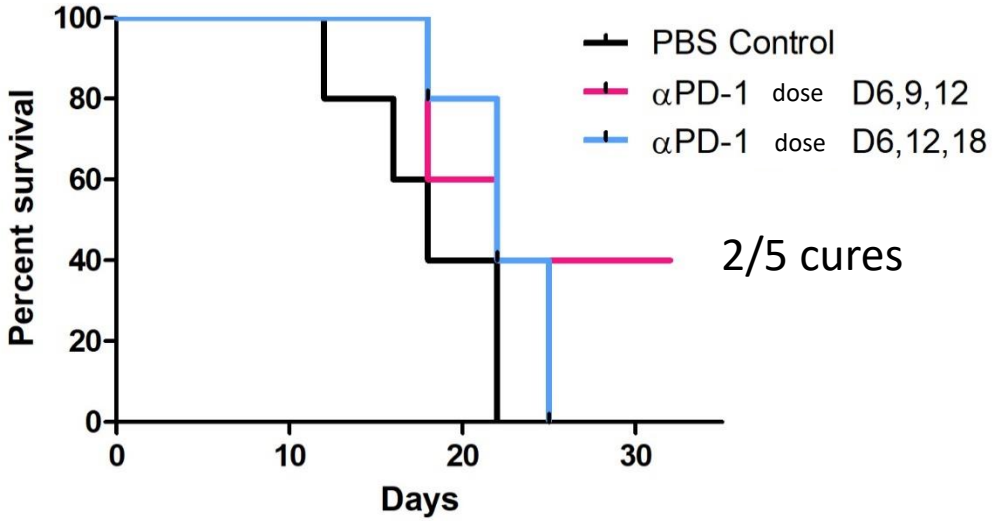


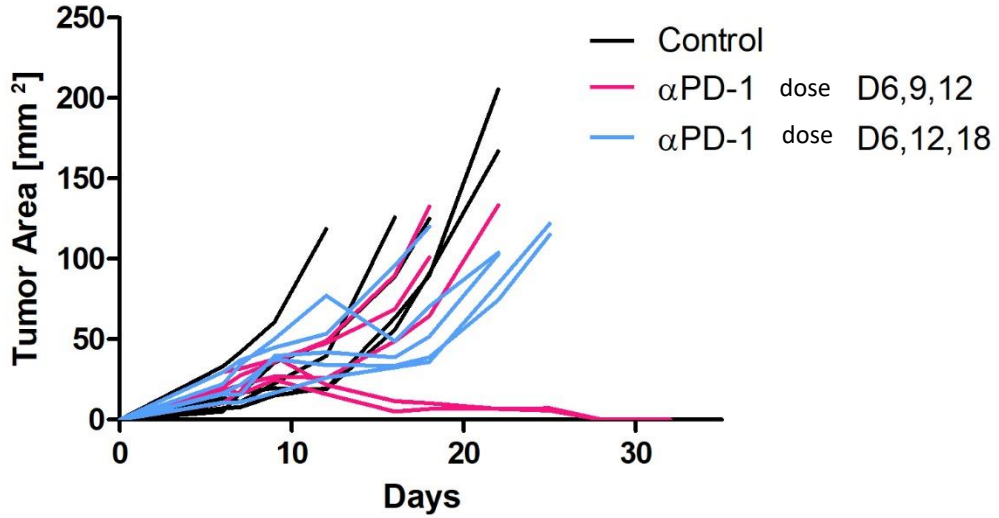
In vivo validation

Next steps:

- Test panel of anti-PD-1 antibodies in vivo
- Using fully murine mouse antibodies, tumor lines
  - Interaction with mouse immune cells
- Translation to humans?







In collaboration with Yash Agarwal

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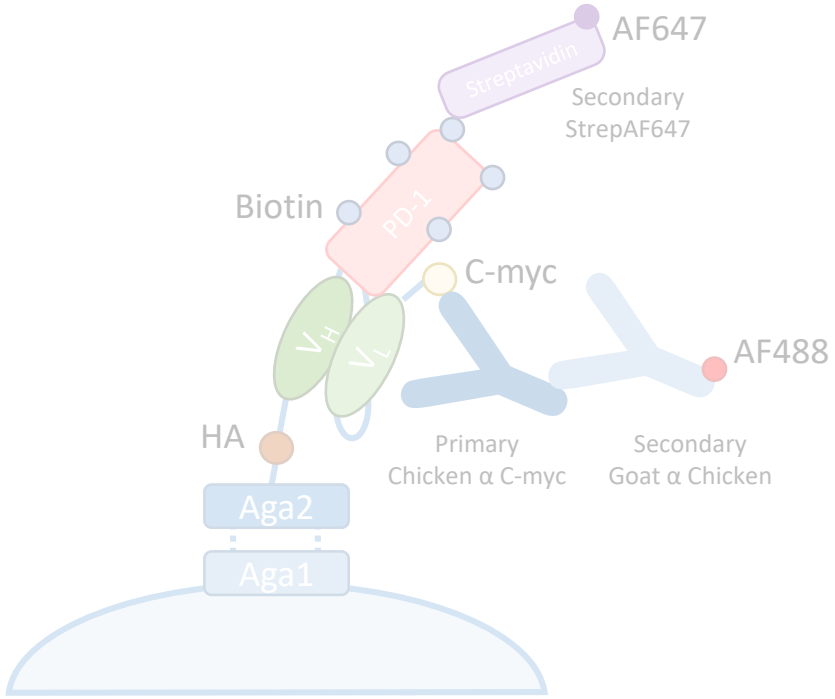
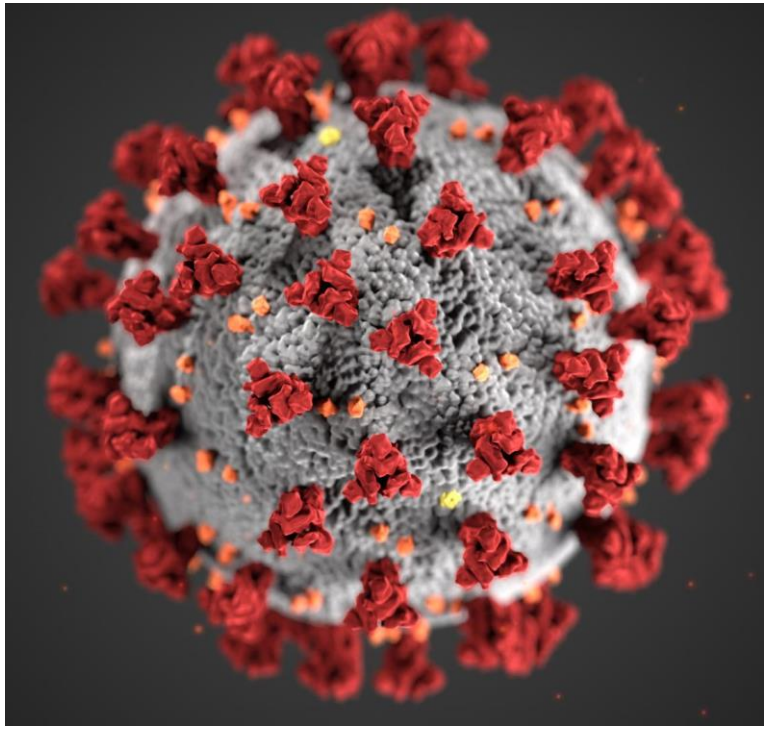


Spotlight on MIT COVID-19 work:

Vaccine, Drug, and Testing Development



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Antibodies and COVID-19

There are three major ways to think about the role of antibodies in COVID-19:

1. Rapid COVID diagnostic test
   - **Sikes Lab**

2. Test for Retained Immunity to COVID-19 – Do patients develop lasting B cell immunity?

3. Antibody Treatment
   - Wittrup Lab → Adimab
   - Synthetic vs. Native Antibody Campaign
   - Other treatments: Remdesivir, tPA (Dr. Mike Yaffe), Pentelute Lab peptide, etc.

4. (Not related to antibodies) Vaccine Development
   - **Love Lab**

5. (Not related to antibodies) RNA Seq Data Set of both diseased and healthy cells expressing ACE2 (the gene encoding the host receptor) and TMPRSS2 (the gene involved in processing the viral spike protein)
   - http://shaleklab.com/covid-19-scrna-seq-resource-datasets-released/

Rapid development of paper-based COVID-19 Immunoassay

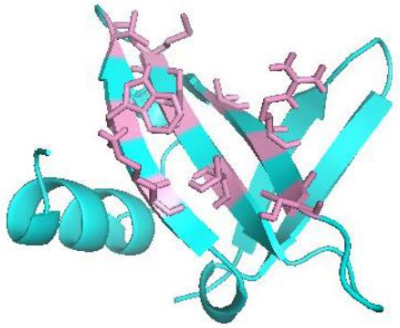
Hadley Sikes Lab

Eric Miller, Ki-Joo Sung, et al.

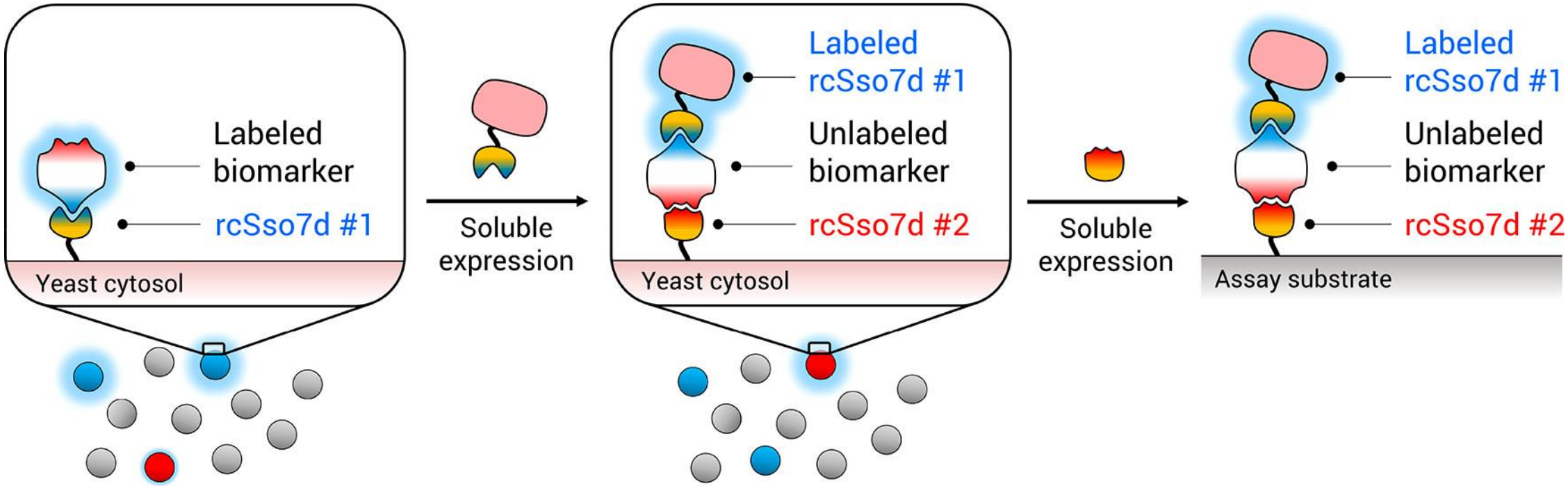
Rapid Development of paper-based COVID-19 Immunoassay

Sso7d vs. Antibody

- 9 amino acid binding pocket
- Thermally stable
- Size

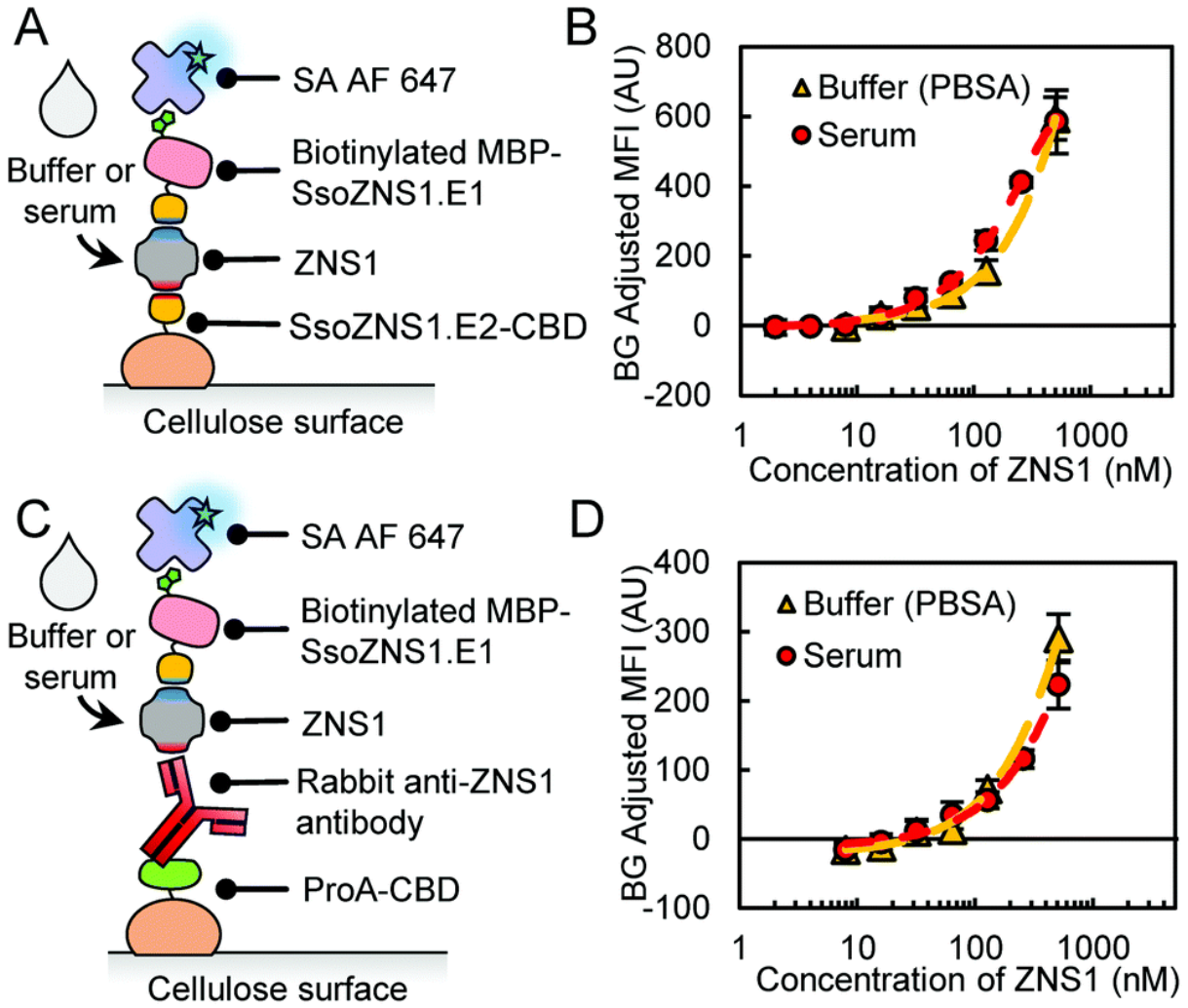


Alison Tisdale, Thesis, 2019



Miller, E. A. et al. *ACS Comb. Sci.*, **2020**, 22, 1, 49-60
Sung, K. et al. *Analyst*, **2020**, 145, 2515-2519

Rapid Development of paper-based COVID-19 Immunoassay



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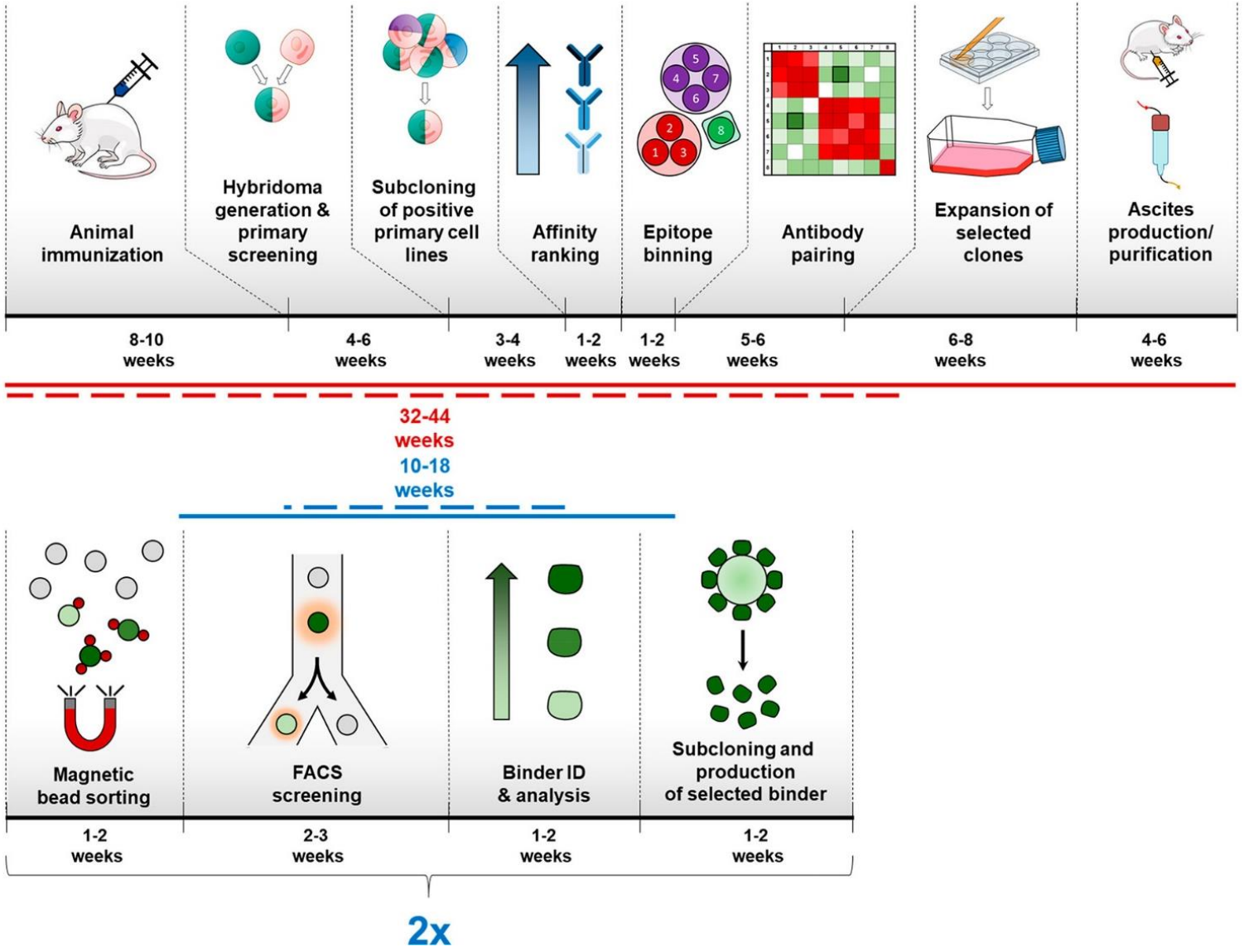
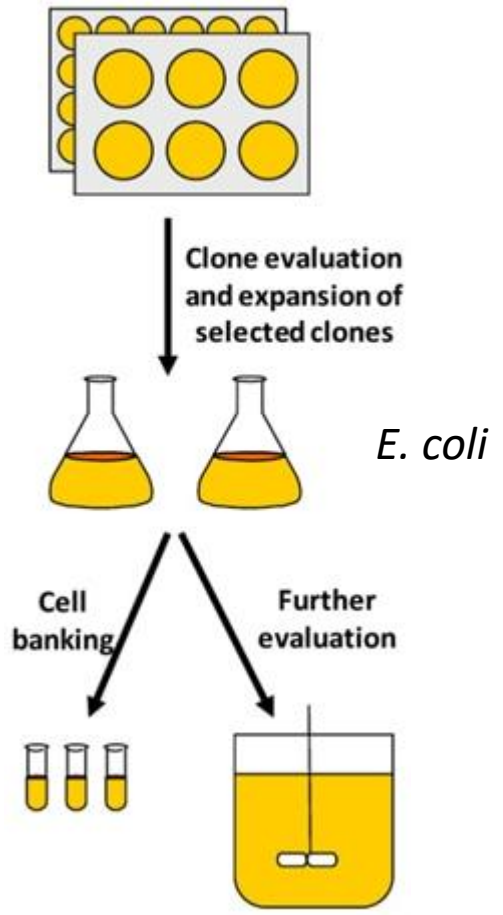




Pharmaceuticals (Basel), 2013

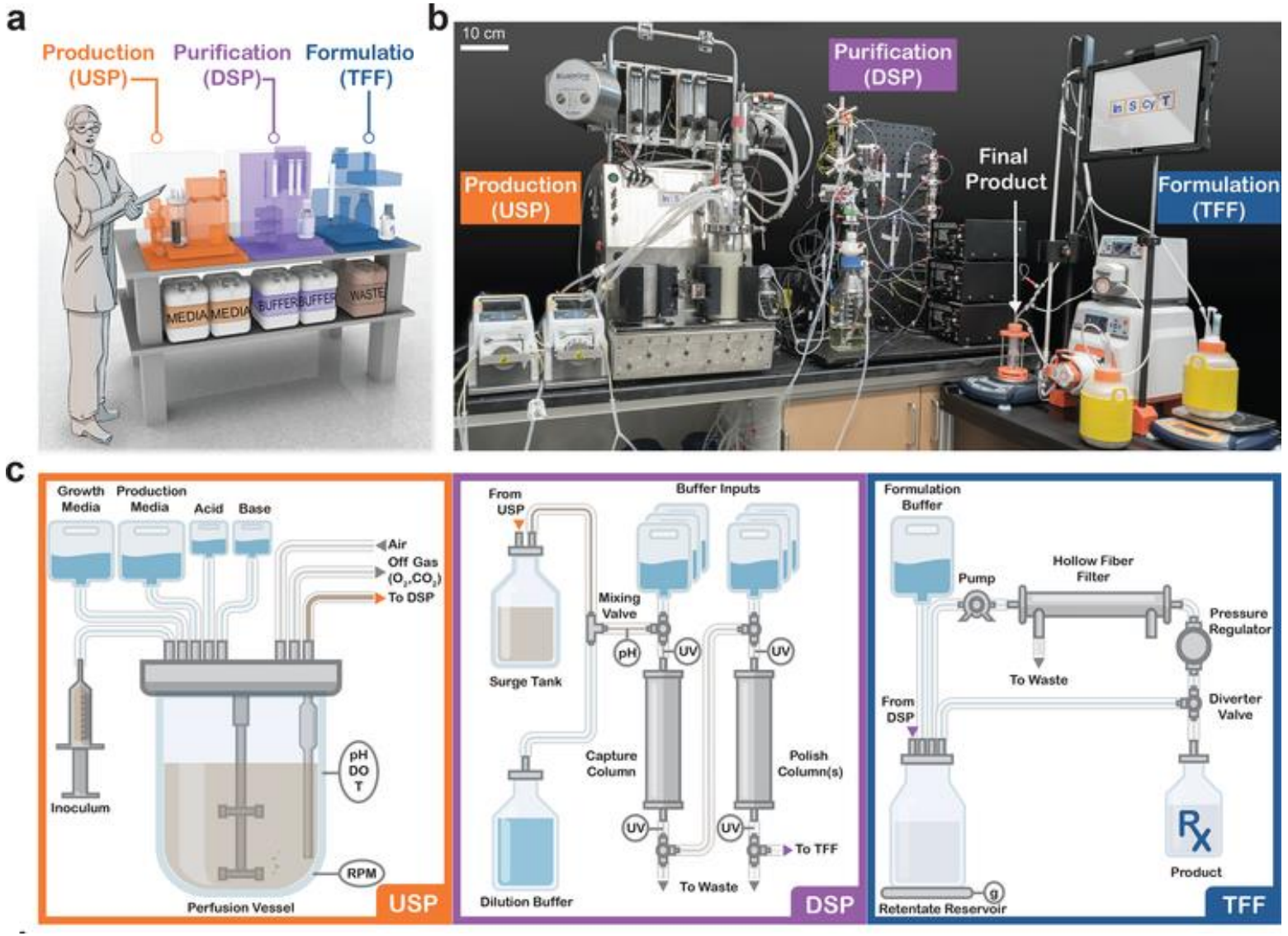
Miller, E. A. et al. *ACS Comb. Sci.*, **2020**, 22, 1, 49-60
Sung, K. et al. *Analyst*, **2020**, 145, 2515-2519

Rapid COVID-19 Subunit Vaccine Development

J. Chris Love Lab

Neil Dalvie, Drew Biedermann, Laura Crowell, Sergio Rodriguez

“Integrated Scalable Cyto-Technology (InSCyT), for the end-to-end production of hundreds to thousands of doses of clinical-quality protein biologics in about three days”



Crowell LE, et al. On-demand manufacturing of clinical-quality biopharmaceuticals. Nat Biotechnol. 2018 Oct 1:10.1038/nbt.4262.

COVID-19 Vaccine Development News (May 2020)

- http://news.mit.edu/2020/mit-love-lab-developing-covid-19-vaccine-designed-reach-billions-0422
  - Love Lab vaccine development at MIT

- https://www.nytimes.com/2020/04/27/world/europe/coronavirus-vaccine-update-oxford.html?referringSource=articleShare
  - Vaccine: Jenner Institute at Oxford, National Institutes of Health's Rocky Mountain Laboratory

- https://www.sciencemag.org/news/2020/04/covid-19-vaccine-protects-monkeys-new-coronavirus-chinese-biotech-reports
  - SinoVac already in human clinical trials

Love Lab Acknowledgements

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Brianna Lax
Keith Cheah
Anthony Tabet
Megan Hoffman
Jordan Stinson
Luciano Santollani

Any questions?

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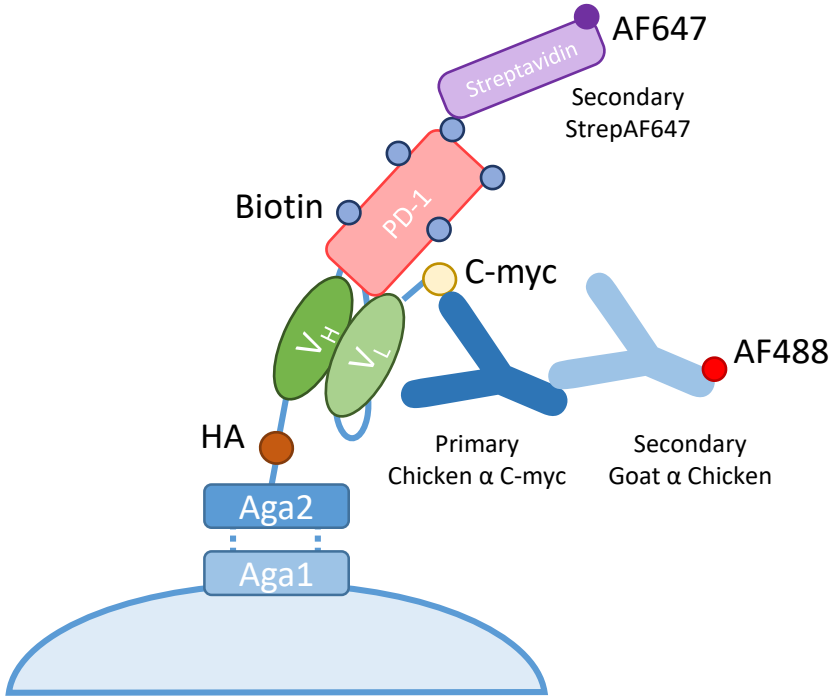

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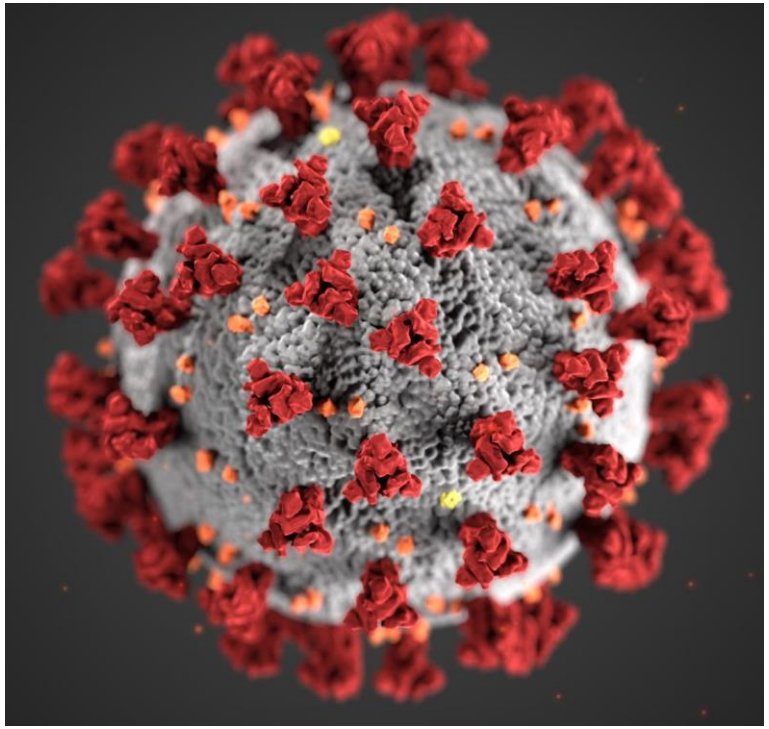

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