ABSTRACT FACE PAGE

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11. **Is this the research presented in this abstract supported by IMAG MSM-related U01 funding? Yes or No**
12. **If the Presenting Author is a trainee, who is the trainee's primary research advisor? Rustom Antia, Ph.D.**

TRAINEE POSTER AND ORAL PRESENTATION COMPETITONS:

New to the meeting this year, we are holding *both* a trainee poster competition and a trainee oral presentation competition! If the presenting author is a trainee (i.e., a student at any level or a post doctoral trainee), he/she may enter his/her abstract in the trainee poster competition, the trainee oral presentation competition, or both competitions. Trainees may also submit more than one abstract to the meeting and enter more than one abstract in these competitions. Prizes will be given to the presenters of the top-ranked trainee oral presentation and the top-ranked trainee poster (judged during the meeting by the Program Committee).

13. **If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Poster Competition*? Yes or No**

*Note: Trainees who enter the poster competition are expected to stand by their poster during the scheduled poster sessions and present them to the judges.

14. **If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Oral Presentation Competition**? Yes or No**

**Note: The Program Committee will select the top four abstracts from trainees who elect to enter their abstract into the trainee oral presentation competition, these four trainees will be notified by Feb. 17th, and they will deliver their oral presentations (which will be judged) on the second day of the meeting after lunch.

MODELING THE IMPACT OF A T CELL-ESCAPING MUTATION ON THE WITHIN-HOST AND POPULATION DYNAMICS OF INFLUENZA A VIRUS

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BACKGROUND: Inactivated influenza vaccines rely on the antigenic match between vaccine and circulating strains, and their effectiveness ranges from 20-70% due to the highly variable antibody epitopes of human influenza A virus (IAV) [1]. T cell-based approaches are candidates for universal influenza vaccines because of (1) the conservation of CD8 T-cell epitopes of IAV and (2) the ability of CD8 T cells to limit severe pathology following IAV infection. We aimed to understand the dynamics of a CD8 T cell-escaping IAV variant by integrating experimental data into models scaled from individual to population levels.

METHODS:
Model. We attempted to infer the epidemiologic viral fitness based on the replicative fitness [2]. The first layer of models relates the transmission fitness to the total amount of virus produced during the infection course, estimated by the area under the curve (AUC) of *in vivo* viral kinetics. The second layer of models qualitatively describe the epidemic potential of the CD8 T cell-escaping variant by integrating the transmission fitness into (1) a population genetics model that incorporates a fitness defect, selective advantage, and frequencies of MHC alleles or (2) an SIRS-based model that further considers compensatory T-cell immunity against the variant.
Experiment. A CD8 T cell-escaping variant (MT) for the immunodominant $NP_{366-374}$ epitope was constructed in the A/Puerto Rico/8/34 (H1N1) (PR8) background. Naïve C57BL/6 mice (B6) or B6 primed 30 days earlier with HKx31 (H3N2) (x31) were infected with a 1:1 mixture of wild-type (WT) and MT PR8. x31 priming was implemented through intranasal (i.n.) or intramuscular (i.m.) routes to dissect the contribution of selection pressure from lung-resident memory CD8 T cells (lung CD8 T_{RM}) versus circulating memory CD8 T cells. Viral loads in the lungs were measured at different time points by droplet digital PCR and were used to construct the *in vivo* viral kinetics.

RESULTS: By comparing the AUCs of the log-transformed kinetics of MT and WT, the selective advantage in transmission was estimated to be 10% in the naïve B6 and 27% in the i.n. x31-primed B6. Interestingly, although the advantage in i.m. x31-primed B6 (22%) was similar to that of i.n. group, the viral load of MT did not deviate from WT until day 6 after challenge [3]. Although measured in inbred mice, these estimates can be viewed as the upper bounds of selective advantage of CD8 T cell-escaping influenza variants in human population. We then integrated these estimates into the population genetics and SIRS models. The models predict that, if the invasion depends entirely on selective advantage, a CD8 T cell-escaping variant requires 5 to 10 years to reach 50% prevalence. Furthermore, depending on the level of compensatory T-cell immunity, the variant may transiently invade but eventually become extinct [4].

CONCLUSIONS: Whether T cell immunity may drive IAV to evolve and escape is a fundamental question for the development of universal influenza vaccines. Our experimental data showed the advantage acquired by escaping one of the immunodominant CD8 T cells is lower than 30%, which corresponds to either extinction or slow invasion within the biologically reasonable parameter space. In addition, the lack of advantage in the i.m.-immunized mice early during infection supports that the lung CD8 T_{RM} impose the majority of selection pressure on the virus. Since lung CD8 T_{RM} decay over time [5], the selection pressure may not be high enough to drive immune escape. We concluded this limited selective advantage may explain the overall conservation of CD8 T cell epitopes of IAV, supporting the utility of targeting these responses in universal influenza vaccine design.

REFERENCES:
1. Belongia et al. *Lancet Infect Dis* (2016) **16**(8):942-951.
2. Wargo and Kurath. *Curr Opin Virol* (2012) **2**(5):538-545.
3. Li et al. *bioRxiv* (2020). doi: 10.1101/2020.01.27.921031
4. Li et al. *J Virol* (2019) **93**(6): e01534-18.
5. Hayward et al. *Nat Immunol* (2020). doi: 10.1038/s41590-019-0584-x

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