Correction

LETTER

The editors note that the name “Rimmelzwaan” incorrectly appeared as “Rimmelzwann” in the title, in line 2 of the first paragraph, and in the first item in the references list. The text has been updated online.

www.pnas.org/cgi/doi/10.1073/pnas.1507470112
Reply to van de Sandt and Rimmelzwaan: Matching epitope display with functional avidity

We appreciate the comments of van de Sandt and Rimmelzwaan (1) on our paper (2), as well as the opportunity to respond.

First, we agree that in Berkhoff et al. (3) single alanine replacements resulted in reduced kinetics of viral replication. Nonetheless, to claim “a reduction of progeny virus of >90%” (1) for all substitutions is misleading. Although figure 1A of Berkhoff et al. shows this at one unspecified time after Madin-Darby canine kidney infection, figure 1B and D of Berkhoff et al., plotting viral titers as a function of time, reveals far less reduction (3). The latter may be more relevant for physiologic infection, where immune mechanisms limit viral replication. The conclusion in the Berkhoff et al. abstract that “alanine replacements for each of the nine amino acids of the M158–66 were tolerated to various extents, except for the anchor residue at the second position” (3) is reasonable and reflected in our report (2). Cao et al. (4) demonstrate that the nuclear export signal motif of the M158–66 epitope and reveals how the nuclear export signal tolerates substantial sequence variability (3). Most interestingly, all mutant viral epitopes tested by chromium release cytolyis assay were no longer targeted by M158–66 cytotoxic T lymphocyte (CTLs) (figure 4M in ref. 3), implying that viral escape from immune recognition could be achieved by mutation within this segment without abrogated M1 nuclear export function. That a high host-cell surface copy number of invariant M158–66 persists during influenza A virus (IAV) infection implies an absence of immune selection pressure against this epitope.

Second, the suggestion that low functional avidity of M158–66–responding T cells was an artifact of peptide stimulation is excluded by the HLA-A2 transgenic mouse study. There, we show (2) that after a primary infection, the bulk polyclonal M158–66 CD8 memory T cells have a functional avidity 1,000-times poorer than that of the protective NP366–374/D5 specificity T-cell population present in the same animal. Such high-frequency M158–66 epitope immunodominance precludes responsiveness to those conserved epitopes. Hence, responses subsequent to in vitro stimulation will be primary in nature and of low avidity. Future development of candidate T-cell epitope-based universal IAV vaccines will allow us to elicit such responses upon in vivo priming, exploring avidity directly or following in vitro secondary stimulation.

Fourth, although Boon et al. (6) nicely show that the magnitude of IAV response is linked to HLA, with HLA-A2 affording the greatest response to specific epitopes using 5-μM peptide concentrations, these data do not speak to the quality of such responses and their relevance to protective T-cell immunity.

In sum, we agree that careful investigation of T-cell responses requires exhaustive analyses, of which physical detection of epitopes is but one part. That said, we caution that emphasis needs to be placed not just on elucidating the frequency of T-cell responses but their quality and, in particular, the match between quantitative epitope display on infected lung epithelium and the avidity of the responding T cells.

Darin B. Keskin\textsuperscript{a,b,c,1}, Bruce R. Reinhold\textsuperscript{a,b,c,1}, Guang Lan Zhang\textsuperscript{b,d}, Alexander R. Ivanov\textsuperscript{f}, Barry L. Karger\textsuperscript{e}, and Ellis L. Reinherz\textsuperscript{a,b,c,1}

\textsuperscript{1}Department of Medical Oncology, Laboratory of Immunobiology, \textsuperscript{2}Cancer Vaccine Center, Dana-Farber Cancer Institute, and \textsuperscript{3}Department of Medicine, Harvard Medical School, Boston, MA 02115; \textsuperscript{4}Computer Science Department, Metropolitan College, Boston University, Boston, MA 02115; and \textsuperscript{5}Barnett Institute, Northeastern University, Boston, MA 02115

\textsuperscript{1}van de Sandt C. Rimmelzwaan GF (2015) Immunodominant responses to the influenza virus M1\textsubscript{58–66} epitope: Stealth or protection? Proc Natl Acad Sci USA 112:E2417.


The authors declare no conflict of interest.

To whom correspondence should be addressed. Email: ellis_reinherz@dfci.harvard.edu.