Impact of competition from self on the efficacy of broadly neutralizing antibodies for HIV

S. M. Ali Tabei [1*], Martin Weigert [2], and Aaron R. Dinner [1]

We use a simple mathematical model to estimate the competition effect of natural self epitopes with HIV gp41 epitopes in binding to HIV broadly neutralizing antibodies. We show that how this competition may influence the viral load in a passive immunization administration, and then discuss the prospect of controlling the viral load with broadly neutralizing antibodies.

***Keywords* — HIV infection, passive immunization, competition, self epitopes, broadly neutralizing antibodies.**

Recently, it was discovered that B cells in humans infected with HIV-1 can produce some rare broadly neutralizing monoclonal antibodies [1]. One antibody, 2G12, was to gp120 [2]. The other antibodies, 2F5 and 4E10, react with conserved membrane-proximal amino acids in HIV-1 gp41 [1]. Trkola *et al.* [2] clinically studied whether these antibodies reduce the viral load in individuals infected with HIV-1 and found that a high dose of the three neutralizing monoclonal antibodies in combination delays viral rebound after cessation of antiretroviral treatment (ART). They also found that passive immunization with these neutralizing antibodies is not effective for reducing the final viral load. Later studies showed fast viral escape from 2G12 by mutation of the gp120 epitope; no such escape from 2F5 and 4E10 was observed [2,3]. Why then is passive administration of these antibodies not capable of reducing the viral load, while for other viral infections such as influenza passive immunization is effective? An answer to this question is crucial for assessing recent efforts to elicit these antibodies through the humoral immune response. In other words, if we could elicit such broadly neutralizing antibodies, then how effective would they be for decreasing the viral load and, in turn, the transmission of infection?

Here, we quantitatively investigate one factor that could limit the impact of cross-reactive broadly neutralizing antibodies on the viral load in vivo. Our study is motivated by the observation that 2F5 and 4E10 also bind a variety of self epitopes. Based on the relative concentration of these self epitopes and their reaction rate with the antibodies, our hypothesis is that these self eptiopes can out compete the viral gp41 epitopes for the antibodies when they are administered passively. In this work, we introduce a mathematical model to delineate the competition hypothesis, estimate quantities that can influence the viral load, and then discuss the prospect of controlling the viral load with broadly neutralizing antibodies that are secreted in an ongoing fashion by activated B cells.

REFERENCES

[1] B. F. Haynes, J. Fleming, E. W. St. Clair, H. Katinger, G. Stiegler, R. Kunert, J. Robinson, R. M. Scearce, K. Plonk, H. F. Staats, *et al.*, "*Cardiolipin Polyspecific Autoreactivity in Two Broadly Neutralizing HIV-1 Antibodies*", Science **308** 5730, (2005)

[2] A. Trkola, H. Kuster, P. Rusert, B. Joos, M. Fischer, C. Leemann, A. Manrique, M. Huber, M. Rehr, A. Oxenius, et al. "*Delay of HIV-1 rebound after cessation of antiretroviral therapy through passive transfer of human neutralizing antibodies*", Nat. Med. 11 , 615–622, (2005)

[3] A. Manrique, P. Rusert, B. Joos, M. Fischer, H. Kuster, C. Leemann, B. Niederöst, R. Weber, G. Stiegler, H. Katinger, et al., *"In Vivo and In Vitro Escape from Neutralizing Antibodies 2G12, 2F5, and 4E10"*, J. Virol. 81, 8793-8808, (2007)

[4] H. Deguchi, J.A. Fernandez, T.M. Hackeng, C.L. Banka and J.H. Griffin, "*Cardiolipin is a normal component of human plasma lipoproteins"*, PNAS, 97(4) 1743-1748 (2000)

Acknowledgements: This work was funded by the HFSP.

[1] James Franck Institute, University of Chicago.
[*] E-mail: tabei@uchicago.edu
[2] Knapp Center for Lupus and Immunology Research, University of Chicago.