

News Flash: Immunosuppressant Surprisingly Enhances Flu Vaccine

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The threat of an influenza pandemic exists largely because of constantly evolving flu viruses that produce new strains every season. The hope of creating a vaccine capable of protecting against multiple flu strains is a focus of a tremendous amount of research. A surprising finding recently reported in *Nature Immunology* by a group of researchers that includes members of the Vaccine and Infectious Disease Division, may contribute much needed knowledge to vaccine development. An immunosuppressant drug, rapamycin, when administered together with a flu vaccine in mice was found to actually improve protection against secondary infections with different flu subtypes.

The quest to develop a 'universal' flu vaccine has been difficult for many reasons. The viral antigens recognized by vaccine-induced immune responses are constantly mutating, resulting in multiple viral subtypes that are capable of evading the immune system. Furthermore, potential immune responses that could offer protection from heterosubtypic infection are poorly understood. Drs. Tomer Hertz, Zachary Wilson and Philip Bradley collaborated on this project with scientists at St. Jude Children's Research Hospital in Memphis Tennessee, revealing some interesting results concerning heterosubtypic protection following vaccination.

The first finding was that rapamycin, when administered together with a vaccine for influenza virus subtype H3N2, was found to protect mice from a secondary lethal infection of several other flu subtypes, including the highly pathogenic H5N1 strain. This effect required the primary flu vaccine, as rapamycin alone did not provide the same protection. Vaccinated mice that were not treated with rapamycin died at a rate of up to 85% following the secondary infection.

Rapamycin, despite being an immunosuppressive drug, has been shown to enhance the generation and quality of memory CD8+ T cells. However, the present study found that these cells were not involved in the rapamycin-mediated protection. On the other hand, the presence of CD4+ T cells and B cells were each found to be required for protection. The rapamycin-induced heterosubtypic protection was long-lasting (up to 6 weeks after primary vaccination), which together with the requirement of CD4+ T cells and B cells, suggested that it was an antibody-mediated effect. This was further demonstrated when serum from rapamycin-treated vaccinated mice provided the same protection when injected in naive mice.

Several other observations unique to the rapamycin-treated mice were made. Antibody class-switching appeared to be inhibited by rapamycin, and this effect was likely caused by limiting both B cell proliferation and the formation of germinal centers, where antibody class switching occurs. These findings were key, as it was determined that the primary effect of rapamycin relevant to heterosubtypic protection was to skew the antibody response away from high-affinity epitopes of the primary vaccinating strain and towards lower affinity antibodies specific for epitopes that happen to be conserved across different flu subtypes. It is believed that following vaccination alone, higher affinity antibodies outcompete lower affinity ones that may be able to recognize multiple strains. By stopping the proliferation of high affinity antibodies, rapamycin allows a broader antibody repertoire to develop, which offers better protection against different flu subtypes. Indeed, the epitopes of the influenza hemagglutinin protein found to be recognized by the antibody response in rapamycin-treated mice differed substantially from those epitopes recognized by the response generated in the control mice (see figure).

"This work may suggest a novel approach to make universal flu vaccines," explains Dr. Hertz. "While significant additional work is required to further study this and we are still far from clinical trials in humans, rapamycin is an FDA-approved drug, and as such may be easier to test in the context of influenza vaccinations in humans." The hope is that through further testing with rapamycin and a better understanding of the characteristics of immune responses to vaccines, we will one day be able to generate a universal flu vaccine that would offer protection against potential pandemic strains.

[Keating R, Hertz T, Wehenkel M, Harris TL, Edwards BA, McClaren JL, Brown SA, Surman S, Wilson ZS, Bradley P, Hurwitz J, Chi H, Doherty PC, Thomas PG, McGargill MA](#). 2013. The kinase mTOR modulates the antibody response to provide cross-protective immunity to lethal infection with influenza virus. *Nat Immunol* 14(12):1266-76.

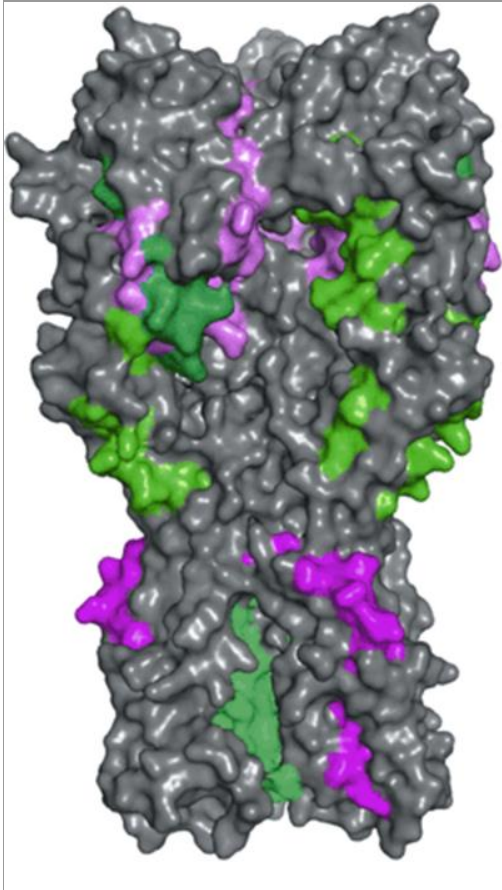


Image provided by Dr. Tomer Hertz.

Following vaccination, rapamycin-induced antibody responses to influenza's hemagglutinin protein recognized different epitopes (purple) with higher conservation across different viral strains, compared to the epitopes recognized by antibody responses in control vaccinated mice (green).