Researchers work to boost effectiveness of the flu vaccine

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Vaccines intended to help the body to fight off the flu bug may actually give the bug an edge, researchers say.

That doesn't mean vaccines are bad, it just may help explain why they aren't as good as they could be, says Dr. Andrew Mellor, director of the Immunotherapy Center at the Medical College of Georgia and Georgia Research Alliance Eminent Scholar in Molecular Immunogenetics.

His team along with viral immunology experts at the University of Georgia believe they can improve the efficacy of flu vaccines - maybe even make them work for more than one flu season - by taking away the bug's advantage.

It's a scenario Dr. Mellor equates to a brake and a gas pedal: when an infection or a vaccine feigning an infection gets the attention of the immune system, the body also mounts a counter-regulatory response to make sure the fighting doesn't get out of hand.

The enzyme, indoleamine 2,3 dioxygenase, or IDO, is part of that response. MCG researchers, led by Drs. Mellor and David Munn, showed in 1998 that fetuses use IDO to avoid rejection by the mother's immune system. IDO's silencing effect is hijacked by tumors and chronic infectious agents like HIV to avoid getting eliminated by the immune response. Acute infections such as the flu, which surface with a vengeance but typically are cleared by the body in a matter of days, appear to subscribe as well.

"We don't even understand the primary response to the influenza infection let alone to a live, attenuated virus used in vaccines," says Dr. Ralph Tripp, viral immunologist, director of UGA's Center for Disease Intervention and Georgia Research Alliance Chair of Animal Health Vaccine Development. "I think if we can understand how IDO regulates the response to viral infections, we can likely build better vaccines."

To better understand both, the researchers are using a flu-infected mouse to identify the lung cells expressing IDO, the signals prompting the expression and the effect on T cells, the orchestrators of the immune response. They also are using different methods to block IDO in the mouse model then see what happens to the infection, the T-cell driven immune response and the immune system's memory of it all.

"We are trying to put together models of who tells who what to do and in what sequence. IDO is somewhere in this chain of events," says Dr. Mellor, the principal investigator on a five-year, $3.1 million grant from the National Institute of Allergy and Infectious Diseases to help dissect IDO's role. "I guess the simplest hope we have is that by manipulating IDO, in this case by blocking it, we can get T cell vaccines to work much better."

A study published in the *Proceedings of the National Academy of Sciences* in March supports the theory. An international team of researchers, led by the University of Melbourne, Australia, showed that a vaccine adjuvant - given to help boost the efficiency of the influenza vaccine - instead boosted IDO expression, hurting the vaccine's ability to provide flu protection.

"This suggests that vaccinologists may have been underestimating the potential efficacy of vaccines because vaccines themselves or adjuvants delivered with vaccines induced IDO that attenuated the host immune response and blunted development of protective immunity," Dr. Mellor

says.

An IDO inhibitor, already in clinical trials for tumors, may be the adjuvant that really gives vaccine a kick, the researchers say.

They believe a sticking point for vaccines generally is that most are designed to activate T cells. While it seems like a logical approach, the fact is most T-cell vaccines don't work that well. Among their many roles, T cells are killer cells that recognize and hopefully eliminate infected cells, which can become infection factories. In fact, scientists believe T cell vaccines should prompt recognition and elimination of different strains of influenza, rather than the Centers for Disease Control and Prevention perennially trying to predict strains for the next flu season and drug makers continuously making new vaccines.

Most viral infections are seasonal and show up looking a little different each year, which is why vaccines vary yearly, notes Dr. Tripp, a professor in the UGA College of Veterinary Medicine. Most influenza infections are mild, accompanied by classic symptoms such as fever and malaise. In fact the general misery associated with the flu is actually the body's response to fighting it. People often mistakenly think the attenuated, or weakened, virus used in the flu vaccine makes them sick when it's actually evidence the body is mounting an immune response, Dr. Mellor says.

Less than 20 percent of influenza infections are severe and a fraction - about 36,000 annually in the United States - go on to cause death. Secondary infections, such as pneumonia, typically contribute to mortality, Dr. Tripp says.

Source: Medical College of Georgia