New Vaccine Prevents CMV Infection and Disease in Mice

June 22, 2007 |

Researchers at the University of California, San Diego (UCSD) Skaggs School of Pharmacy and Pharmaceutical Sciences have patented a strategy for developing a human vaccine to prevent against Human Cytomegalovirus (hCMV) infection and disease.

CMV, a type of herpes virus, is the leading viral cause of birth defects and a serious problem in patients with compromised immune systems. The body's natural immunity doesn't protect against infection by the virus, estimated to be present in 50 to 75 percent of all adults.

"Until now, scientists haven't been able to develop a vaccine to protect against CMV," said Deborah H. Spector, Ph.D., UCSD Professor of Cellular and Molecular Medicine and faculty member of the Skaggs School of Pharmacy and Pharmaceutical Sciences. "Using a two-pronged approach, we successfully created and tested a vaccine in a mouse model with CMV that shows enormous promise for re-directing the body's immune system, enabling it to fight the virus."

The mouse vaccine generates an immune response that protects against both infection and development of disease when the virus is present by completely disarming the virus's ability to replicate and establish a persistent infection. The work is currently online in advance of publication in the July issue of *Journal of Virology*.

"Our approach generates an immune response that is different from the normal response to the virus, and we hope to have found an 'Achilles' heel' in the defenses that the virus uses to evade the immune system," said Spector. "The virus has evolved to persist in the host by evading the immune responses either by hiding or by misdirecting the host's immune responses. We found a way to teach the host immune system to not be tricked by the virus." She added that the next step is to apply this strategy to create a vaccine for use in humans.

CMV is a virus that, while carried by the majority of adults in the United States, can remain dormant for years, if not the lifetime, of a healthy individual. However, two percent of all children are born with the virus passed on by the mother *in utero*, and 15 percent of those children will show symptoms such as hearing loss, mental retardation, motor or learning disabilities. Because

the host's natural immune system can protect from the disease but can't rid the body of the virus, people remain infected and can become re-infected or infect others through saliva.

"Children in day care settings, for example, or adults who are sexually active, can pass along the virus," explained Spector. "It becomes a serious problem in developing infants during the pregnancy or in those whose immune system is compromised, such as AIDS or transplant patients."

When a persistent virus such as CMV infects an individual, it disarms the host immune system in two ways – by hiding or masking the proteins that would normally provoke an immune response, or by fooling the immune system into mounting a response that doesn't work to eradicate the virus.

"We needed a way to make the host defense system sit up and take notice," said Christopher S. Morello, Ph.D., first author of the study.

To do this, the researchers devised a vaccine with a one-two punch that combines a DNA immunization that targets T-cells to essential genes required for CMV replication, with a killed virus that prompts the body's B-cells to generate an antibody response.

The vaccine contains the DNA of two essential genes that are essential for replication of the virus. These genes – which are also found in other herpes viruses such as chicken pox or herpes simplex – have the same or very similar sequence, structure and function whether in human or mouse viruses, and present a novel target for the host's T-cells to muster forces and attack the virus. Secondly, the vaccine also contains a "boost" from an inactivated virus, which generates an antibody response. Neither approach alone would give complete protection.

"In mice, the vaccine not only fought the disease, but prevented the infection from being established in the first place," Morello said.

Researchers at UCSD hope to begin pre-clinical work on development of a human vaccine. If successful, an FDA-approved, commercially licensed hCMV vaccine could be administered to specific at-risk populations, such as females prior to child-bearing years, day care providers, organ transplant recipients, or as part of regular childhood immunizations.

"This approach may also be valid for a number of diseases associated with persistent or latent infections, including all types of herpes-associated diseases, AIDS, or hepatitis," said Spector. These viruses persist because immune responses generated by the viral infection are not able to eradicate the virus.

Additional contributors to the paper include Laura A. Kelley of the UCSD Division of Biological Sciences; and Michael W. Munks and Ann B. Hill, Department of Molecular Microbiology and

Immunology, Oregon Health and Science University. The research was funded by the National Institutes of Health and the March of Dimes.

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