Discovery may help defang viruses

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Researchers may be able to tinker with a single amino acid of an enzyme that helps viruses multiply to render them harmless, according to molecular biologists who say the discovery could pave the way for a fast and cheap method of making vaccines.

"We have successfully tested this technique with poliovirus," said Craig Cameron, the Paul Berg professor of biochemistry and molecular biology at Penn State. "And we think it is applicable to most other viruses." Viruses have a simple mission; infect a cell, make more viruses, and then break out of the cell to infect more cells. This calls for fast and efficient multiplication. Viruses do this with the help of an enzyme called polymerase, whose main job is to assist in making more copies of the virus.

Once a virus infects a cell, there is a race against the clock between the virus, which is trying to multiply quickly, and the immune system trying to control the spread. A virus can cause disease and death if it can spread more rapidly than the immune system can neutralize it.

But if the body has been exposed to a vaccine – weakened form of the virus in this case – the body can respond more rapidly when it is exposed to the virulent strain. The key to developing vaccines is finding the one strain – mutation – that will prime the immune system without causing disease.

The Penn State researchers may have done just that. Cameron and his colleagues, Jamie Arnold and Christian Castro, both research associates,

have identified a key amino acid in the polymerase of poliovirus that controls the speed and accuracy with which the virus is able to multiply.

By replacing this key residue with different amino acids, the researchers were able to generate mutants of the virus that are essentially harmless.

"We found that very subtle changes in the chemistry at this location of the polymerase has dramatic effects on weakening the virus," said Cameron, who has a provisional patent on the technique.

When lab mice are infected with these mutant strains of the virus, it takes a lot more of the virus to sicken, or kill the animals. Cameron says tests suggest that some viral strains with specific mutation patterns lead to a form of the virus that cannot sustain itself.

"By altering a single lysine residue, you not only affect the virus' replication, but also the accuracy with which it is copied," he said. "A virus' replication speed and accuracy is optimized; there is a delicate balance. We have defined the optima for poliovirus but where that balance is going to be for different viruses, we do not yet know."

Since all viruses have a similar mechanism regulating their replication, Cameron says the discovery may represent a universal mechanism of weakening other viruses causing diseases such as influenza, SARS, Dengue fever and the West Nile Virus for developing vaccines.

"All standard approaches for vaccine development take years," said Cameron. "It is all a random trial and error process to get an attenuated – weakened – virus that may be treated as a potential vaccine candidate. There is no direct method."

Positive strand RNA viruses – those with only one gene – such as SARS coronavirus, and hepatitis C virus compound the problem. "The gene

makes a protein that gets processed into a lot of different functions," said Cameron. "There is no gene to delete." But these viruses do have an amino acid similar to the residue identified in poliovirus, which can be replaced to produce weak variants. These new strains are quickly neutralized by the immune system, providing protection against the more virulent strains.

The Penn State Scientist says his findings could help avoid the long time it takes to create vaccines, and might help mount a more effective response against ever-changing viruses such as influenza, as well as emerging and re-emerging viruses such as SARS coronavirus, West Nile Virus and Dengue virus.

He added that the technique of quickly creating weak viral strains for use as vaccines could also protect against viruses such as Ebola and smallpox, which might be used as biological weapons.

Source: Penn State