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Researchers determine 3D structure of adeno-associated virus 9: Aim to boost gene therapy

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A team of researchers led by the University of Florida, Gainesville, has determined the precise structure of a virus that has promise as a delivery vehicle for gene therapy. The research appears in the June 2012 issue of the *Journal of Virology*.

Adeno-associated viruses are benign in humans, and are highly promising in gene therapy as delivery devices to place healthy genes into the genome, in order to compensate for malfunctioning genes. These viruses come in 12 different serotypes (sets of antigens). Adeno-associated virus 9 (AAV9) is currently under development as a delivery vehicle for treating neurodegenerative diseases, such as spinal muscle atrophy, amyotrophic lateral sclerosis, and Parkinson's disease.

Mavis Agbandje-McKenna of the University of Florida, Gainesville and her colleagues have determined the precise structure of AAV9, work she says "will help us to understand which parts of the capsid we can alter or modify to make safer, more efficient vectors, and which regions should not be modified as we try to engineer capsids to treat specific diseases." The capsid is the shell that protects the viral nucleic acid.

The researchers applied X-ray crystallography, the technique that was used to determine DNA's structure nearly 60 years ago, as well as a complementary, and much newer technique called cryo-electron microscopy and image reconstruction, to determining AAV9's structure. That work revealed the precise position in space of every atom of the AAV9 capsid. They then compared that structure to other adeno-

associated viruses for which structures have been determined, and identified which regions are conserved, and which vary, in comparison to AAV9. They then annotated these regions with respect to function: different parts of the capsid are involved in different functions such as receptor attachment, determining the efficiency of transduction in specific tissues, and antibody recognition.

“Our goal is to use 3D information to inform the design of gene delivery vectors that will have improved efficacy with respect to tissue targeted delivery of therapies, and reduced host immune antibody response recognition,” says Agbandje-McKenna. “The information that we have obtained is guiding further research in our group as well as groups elsewhere who are trying to understand the functions of the capsid, in an effort to improve gene delivery via AAV.” She notes that AAV9 is especially important in these areas because of its ability to cross the blood brain barrier, adding that this makes it particularly useful for treating brain diseases, “for which current therapies are quite limited.”

More information: M.A. DeMattia, H.-J. Nam, K. Van Vliet, M. Agbandje-McKenna, et al. Structural insight into the unique properties of adeno-associated virus serotype 9. *J. Virol.* 86:6947-6958.

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