

W0168

Crystal Structure of AAV8 and Structural Implications of Acidification. H Nam¹, M Lane¹, B Gurda-Whitaker¹, R McKenna¹, S Zolotukhin², N Muzyczka³, M Agbandje-McKenna¹, ¹Dept. Biochemistry and Molecular Biology, ²Dept. Pediatrics, ³Dept. Molecular Genetics and Microbiology, College of Medicine Univ. of Florida Gainesville, FL 32610.

Transduction of Parvoviruses into host cells depends on endosomal processing, and its mechanisms, including the effect of low pH on viral capsids, are poorly understood. Adeno-associated viruses (AAVs), members of the *Parvoviridae*, are being actively investigated as gene therapy vectors. AAV serotype 8, in particular, is a promising candidate for liver targeted gene therapy. We have determined the crystal structure of the AAV8 viral capsid at four different pHs, 7.5, 6.0, 5.5, and 4.0, that represent pHs of endosomal compartments. The general fold of the AAV8 is similar to those of previously determined AAVs. The most pronounced differences in AAV8 compared to other AAVs reside in regions near the three-fold axis that are important for receptor binding and host cell tropism. Structural variations at different pHs are also observed at the interior and exterior surfaces of the three-fold capsid region. Our studies are identifying specific capsid regions responsible for AAV8's preferential tropism for liver cells, and the structures at various pHs aid our understanding of the effects of endosomal processing on AAV viral capsids.