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Structure of Adeno-Associated Virus 1 to 8.6 Å resolution by Cryo-Electron Microscopy. E.B. Miller¹, B. Gurda-Whitaker¹, L. Govindasamy¹, X. Yan², R. McKenna¹, S. Zolotukhin³, N. Muzyczka⁴, T.S. Baker², M. Agbandje-McKenna¹, ¹Dept. of Biochem. & Mol. Biol., ³Dept. of Pediatrics, ⁴Dept. of Mol. Genetics and Microbiology, COM, UF, FL 32610; ²Dept of Chem./Biochem. & Mol. Biol. UCSD, CA 92093.

Adeno-associated viruses (AAV) are non-pathogenic ssDNA parvoviruses. Members of this genus require co-infection with a helper virus for successful replication. Recombinant AAV (rAAV) show great potential as vectors for therapeutic gene delivery. *In vitro* and *in vivo*, rAAV1 vectors show superior transduction of muscle cells compared to rAAV2, despite being ~83% identical to the latter virus at the amino acid sequence level. Thus the need for rational selection of an appropriate AAV serotype for tissue specific gene therapy applications has generated interest in the structural features of the capsids responsible for capsid-tissue interactions. Towards mapping the AAV1 capsid features responsible for its enhanced muscle transduction, we have determined its structure to 8.6 Å resolution by cryo-electron microscopy and image reconstruction. A pseudo-atomic model of the AAV1 capsid VP has been built into the reconstructed density based on the crystal structure of AAV2. Comparison of the surface topology of the AAV1 capsid with those available for AAV2, AAV4, AAV5, and AAV8 will be presented.