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Interactions of AAV-2 with its Cellular Receptor (AAVR), Visualized by *Cryo*-Electron Microscopy

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Recently, a receptor essential for cellular transduction by most AAV serotypes has been identified as AAVR, through an unbiased genome-wide screen. AAVR is a multi-domain transmembrane protein, observed transiently at the cell surface, but predominantly in the *peri*-nuclear region of the *trans*-Golgi network, and trafficked endocytotically like the AAV virus. Various *ecto*-domain constructs have been expressed heterologously, including various combinations of the five polycystic kidney disease domains. (PKD domains are often involved in protein interactions.) Several competitively inhibit cellular transduction by AAV and/or have nano-molar avidities as measured by surface plasmon resonance. Interactions are serotype-dependent: AAV-2 interacts most strongly with PKD domain 2, whereas AAV-5 has stronger interactions with PKD domain 1. Hybrid biophysical approaches are revealing the structure of the AAV2-AAVR complex. A combination of *cryo*-electron tomography at about 30Å resolution, single particle *cryo*-electron microscopy with sub-volume averaging at 10Å resolution, together with cross-linking analysis, indicate tight binding at a subset of symmetry related sites on the virus, with distal receptor domains posed in several discrete configurations. With a divide-and-conquer strategy we are beginning to visualize parts of the receptor at approaching 3Å resolution, the point at which atomic models can be fit to reveal the molecular interactions.