contrast, Vps4 dimerization is inhibited by a series of different mutations within the interface used to form the continuous helix (e.g., I351A, I354D, L151D and W388A). This leads to the surprising conclusion that the Vps4 dimer is likely formed by an asymmetric interface. We suggest that this interface likely resembles, but is not identical to, the asymmetric dimer interface that mediates Vps4 helix formation in all crystal forms reported to date. If correct, this model begs the question why the interaction does not repeat infinitely to form a helical (or linear) polymer in solution. Our preferred explanation is that the two subunits of the asymmetric dimer have different interdomain angles, making the dimer incompatible with repeating interactions. This type of asymmetric interaction is hinted at in the crystal structure of the Vps4-ATPγS complex, where differing interdomain angles in the three different subunits produce distinct dimeric interactions between the A:B, B:C, and C:A molecule pairs. However, a more precise understanding of this structure will clearly require high resolution crystals of a discrete Vps4 dimer.

High resolution structural studies will also be required to reveal the precise conformation of the Vps4 dodecamer. In this case, however, moderate resolution cryo-EM reconstruction of dodecameric Vps4 assemblies are available, and these structures reveal that the two hexameric rings adopt very different conformations[31]. The structure of the more constricted ring appears to be consistent with a homology model based upon the hexameric ring formed by the D1 AAA ATPase cassette of the related p97 ATPase[47]. Although the resolution of the $Vps4_{\Delta MIT}$ reconstruction is modest (~25Å), the homology model matches the reconstructed ring in overall shape and dimensions, and the six Vps4 β-domains appear to protrude from the exterior of