PRMT5 is an essential arginine methyltransferase and a therapeutic target in MTAP-null cancers. PRMT5 uses adaptor proteins for substrate recruitment through a previously undefined mechanism. Dr. Mulvaney and her research colleagues demonstrate that PRMT5 uses modular adaptor proteins containing a common binding motif for substrate recruitment, comparable with other enzyme classes such as kinases and E3 ligases. The researchers structurally resolve the interface with PRMT5 and show via genetic perturbation that it is required for methylation of adaptor-recruited substrates including the spliceosome, histones, and ribosomal complexes. Furthermore, disruption of this site affects Sm spliceosome activity, leading to intron retention. Genetic disruption of the PRMT5-substrate adaptor interface impairs growth of MTAP-null tumor cells and is thus a site for development of therapeutic inhibitors of PRMT5.