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ON THE COVER
A screen of dimeric compounds based on antimalarial heterocycles identified the anticancer compound DQ661, which concurrently inhibited lysosomal catabolism and mTORC1 signaling. DQ661 bound to the lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1), which promotes proteolysis of palmitoylated proteins, and PPT1 inhibition phenocopied DQ661 treatment, resulting in palmitoylated protein accumulation and reduced mTORC1 signaling and lysosomal catabolism. In vivo, DQ661 could be combined with chemotherapy, and it suppressed the growth of melanoma xenografts and mouse colon and pancreatic tumors. The identification of DQ661 demonstrates that inhibitors concurrently targeting both mTORC1 signaling and lysosomal catabolism can suppress tumor growth. For details, please see the article by Rebecca, Nicastri, McLaughlin, and colleagues on page 1266.