We previously demonstrated that PHLD3 is a novel tumor suppressor of pancreatic neuroendocrine tumor (PanNET), and showed hyperplasia of the pancreatic islets is found in PHLD3 deficient mice. We also showed that in addition to PHLD3, functional loss of MEN1, which is a tumor suppressor gene associated with multiple endocrine neoplasia type 1, is required for the development of PanNET (PNAS, 2014). The mechanisms of PanNET tumorigenesis remain unclear to date because of the shortage of proper experimental model systems. Therefore, we established a new PanNET mouse model that is deficient in both PHLD3 and MEN1 (DKO) and analyzed the development and progression of PanNET. While less malignant PanNET were found in MEN1 single–deficient mice at a later age as previously reported, more malignant PanNET were found at an earlier age in DKO mice. These data suggest that the PanNET-suppressing pathway of PHLD3 and MEN1 are independent and the functional loss of PHLD3 is the critical determinant of PanNET progression. Using the DKO mice, we are now investigating the detailed molecular mechanism of PanNET tumorigenesis and the effects of the anti–PanNET drugs.