KRAS is one of the most frequently mutated genes in non-small cell lung cancer (NSCLC) and pancreatic ductal adenocarcinoma (PDAC) and therefore an appealing target for new targeted therapy approaches. However, all recent efforts to target *KRAS*-mutated tumors failed so far in clinical settings, but multiple potential approaches are under investigation. As direct targeting of KRAS is difficult, indirect approaches should be considered. Latest sequencing efforts have unraveled the mutational landscape of NSCLC and PDAC tumors. Next to *KRAS* mutations, a lot of other genes are found to be mutated within the same tumor. Both NSCLC and PDAC harbor recurrent functional mutations of the master DNA damage response (DDR) kinase ataxia telangiectasia mutated (ATM), a key kinase in homologous recombination (HR). Although mutations in HR genes predispose to the development of cancer by increased genomic instability, they also increase the dependence of cancer cells on other repair mechanisms and drive a tumor more sensitive to certain DNA damaging agents and other targeted therapies.

Here we evaluated in two different *Kras*-mutant mouse models how ATM deficiency affects tumor progression and response to therapy. Two targeted therapy approaches could be established in ATM-deficient tumors, namely the PARP inhibitor olaparib as well as the ATR inhibitor VE-822. Taken together, our results provide a functional rationale to profile human tumors for disabling *ATM* mutations and for the use of PARP and ATR inhibitors to potentially improve treatment in *ATM*-mutant NSCLC and PDAC.