Therapies that induce DNA replication stress are the foundation of many cancer treatment regimes. We have used chemical-genetic CRISPR-Cas9 screens to reveal genes that modulate sensitivity to the nucleoside analog gemcitabine. I’ll discuss novel roles of APOBEC3 family cytidine deaminases in promoting replication stress resistance in pancreatic cancer cells, and the prognostic potential of gemcitabine sensitivity modulators that we have identified.