A chemical degron system for exploring PALB2 synthetic lethal combinations

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Cells with poorly functioning homologous recombination (HR) are extremely sensitive to poly (ADP-ribose) polymerase (PARP) inhibition. Current approaches to exploit this vulnerability focus exclusively on PARP inhibition in a mutated HR genetic background. If HR factors could be inhibited or degraded in normal cells with drugs, then combination treatments of these agents with PARP inhibitors could open new patient populations to this well-validated combination. Here we build a model system which fully recapitulates PARP/HR synthetic lethality by installing a small-molecule responsive zinc-finger degron in the HR factor partner and localizer of BRCA2 (PALB2). We also then test a battery of peptide ligands for PALB2 based on its natural binding partner. Taken together these our studies validate PALB2 as a target for drug development and provide the tools for identifying small molecule binders.