Three years ago Patricia LoRusso, DO, Professor of Medicine and Associate Director of Experimental Therapeutics at Yale Cancer Center, was drawn to Yale in part because of the strong basic science work done here. The group investigating DNA damage repair (DDR) especially impressed her, but she noticed that little of their work had made the jump from the lab to the clinic. Once she arrived, she began looking for ways to change that.

Around the same time, the FDA approved a new drug called olaparib, a PARP inhibitor. PARP inhibitors are a group of proteins crucial to the repair of damaged DNA. If defective DNA isn’t fixed or removed, the cell weakens and often dies. PARP inhibitors harness cell death by blocking DNA repair. BRCA mutations are associated with several cancers, including ovarian, breast, pancreatic, and prostate cancers, as well as others. Olaparib stops BRCA-deficient tumor cells from repairing their DNA, causing further deterioration and cell death.

Dr. LoRusso had done clinical trials on PARP inhibitors before coming to Yale. Yale’s DDS group was deeply involved in research about the mechanisms of DNA repair. “I got a call from Dr. Joann Balazs Sweasy, who was a clinical trial based on the concept, which was approved by the NCI’s Experimental Therapeutics Clinical Trials Network (ETCTN). Dr. LoRusso is now enrolling patients. The one current project originated when Dr. LoRusso put two observations together. Clinical research had shown that only about 15 percent of women with triple negative breast cancer responded to immunotherapy inhibitors—immunotherapy drugs. Other clinical research, done after genetic profiling of tumors became common, showed that about 15 percent of women with breast cancer have BRCA mutations.

“No, my thought was,” explained Dr. LoRusso, “could these 15 percent responders to immunotherapy inhibitors actually be patients who had BRCA mutations? And if we treated BRCA-mutant patients with a PARP inhibitor, could we increase the responsiveness of the tumor to immunotherapy inhibitors?”

To investigate this idea she formed a team of basic scientists, translational scientists, and clinicians. They weren’t looking for PARP inhibitors, including olaparib, to create clinical trials on PARP inhibitors before coming to Yale. Yale’s DDS group was deeply involved in research about the mechanisms of DNA repair.

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“Immunotherapy reactivates the immune system and recognizes these neoantigens as targets to kill the tumor cells.” Her lab is testing this hypothesis on mouse models and human cancer cell lines. The calls the results encouraging for patients. To investigate this idea she formed a team of basic scientists, translational scientists, and clinicians. They weren’t looking for PARP inhibitors, including olaparib, to create clinical trials on PARP inhibitors before coming to Yale. Yale’s DDS group was deeply involved in research about the mechanisms of DNA repair.

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