“One of the burning questions in contemporary cancer research is, ‘What are the critical therapeutic targets that uncouple aberrant growth and survival?’ I am employing viruses to pin down key cellular processes that are dysfunctional in cancer cells and to develop novel, virus-based cancer therapies.”

If a cell suffers non-repairable injury to its genetic material, or cell growth starts to go astray, the tumor suppressor protein 53 pulls the emergency brake, a built-in “auto-destruct” mechanism that eliminates abnormal cells from the body before they can cause disease, including cancer. To sidestep the cell’s suicide program—a process called apoptosis—tumor cells need to inactivate p53, which turns on genes that mediate cell cycle arrest and apoptosis.

Similarly, adenovirus, which causes upper-respiratory infections, needs to get p53 out of the way to multiply successfully; therefore it brings along a viral protein, E1B-55K, which binds and degrades p53 in infected cells. Without E1B-55K to inactivate p53, adenovirus should only be able to replicate in p53-deficient tumor cells, making it the perfect candidate for oncolytic cancer therapy. Oncolytic viruses offer a novel and potentially self-perpetuating cancer therapy: Each time a virus infects a cancer cell and successfully multiplies, the virus ultimately kills the cancer cell by bursting it open to release thousands of viral progeny. The next generation seeks out remaining tumor cells and distant micro-metastases but leaves normal cells unharmed.

Clinical trials found such viruses to be safe and promising. Contrary to all expectations, however, patient responses did not correlate with the p53 status of their tumors. When O’Shea followed up on this unexpected finding, she discovered that the inability of the E1B-55K-mutant virus to replicate in normal cells was not because the virus failed to degrade p53. Instead, adenovirus brings along another protein, E4-ORF3, which neutralizes the p53 checkpoint through a completely different mechanism. It prevents p53 from binding to its target genes in the genome by modifying histone proteins, the “spools” around which DNA winds. With its access denied, p53 is powerless to pull the trigger on apoptosis. O’Shea and her team are now exploiting this new viral protein as a powerful tool to both pinpoint and connect critical new targets in the cellular p53 tumor suppressor network and to develop the next generation of oncolytic viruses.

For more information, please visit www.salk.edu/faculty/o’shea