New Drug Combination Shows Promise Against Pancreatic Cancer

A combination of three immunotherapy drugs shows promise in animal studies.

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Pancreatic cancer, which will affect an estimated 60,430 Americans this year, is notoriously hard to treat. Chemotherapy and immunotherapy drugs sometimes work at first, but often the tumors develop resistance and continue to grow. This makes it one of the most lethal types of cancer, with the average five-year survival rate after diagnosis hovering around 10%.

Against the backdrop of these distressing statistics comes exciting news from MIT, where a team of researchers has developed a new therapeutic approach that may bring relief to thousands of patients. The team, including former Damon Runyon Fellow Peter Westcott, PhD, has uncovered a combination of three immunotherapy drugs that can eliminate pancreatic tumors in mice.

One of the most common forms of immunotherapy is called an immune checkpoint inhibitor. These drugs block proteins on the surface of cancer cells from binding to receptors on immune T-cells and turning those immune cells “off.” One such drug, which blocks the protein PD-L1 on cancer cells from binding to the “off switch” known as PD-1 on T-cells, has shown remarkable success in treating a range of cancers, but frustratingly little effect on pancreatic cancer.

For a time, researchers suspected this was because pancreatic cancer cells presented fewer mutated proteins on their surface, making them less recognizable to T-cells, even when those T-cells are active. But upon closer inspection, it appears pancreatic cancer cells have plenty of red-flag mutant proteins protruding from their membranes. What they do have fewer of are PD-L1 proteins—indicating that they “turn off” T-cells by different means.

Further investigation of the pancreatic cancer genome revealed high expression of a protein called CD155, which binds to a receptor on T-cells called TIGIT and induces what is referred to as “T-cell exhaustion.” As the term implies, a T-cell in this state may identify a tumor cell but fail to launch an attack, like a sleepy security guard pointing a finger at a shoplifter as she exits the store.

Following this discovery, the researchers began to test whether PD-1 and TIGIT inhibitors combined could do what either drug alone cannot—prevent pancreatic cancer cells from disabling immune cells.

To this cocktail they added one more ingredient: a drug called the CD40 agonist antibody, which

has been shown to stop pancreatic tumor growth (but not shrink them) when combined with either a PD-1 or TIGIT inhibitor. To the team's immense excitement, the three drugs together shrunk pancreatic tumors in half the mouse recipients and completely eliminated them in a quarter, with no sign of regrowth.

Each of the constituent drugs is currently in Phase 2 clinical trials, and the team is working hard to bring the triple combination to clinical trials later this year. Thanks to their efforts, the list of viable treatment options for pancreatic cancer patients may grow longer soon.

Read more in Cancer Cell.

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