MARK WASHBURN

Noelle has created an experimental cancer vaccine that stimulates both the innate and acquired immune systems.

Two-pronged cancer vaccine shows promise

Humans have two immune systems, explains Randolph Noelle, Ph.D. So it makes sense to take advantage of both when developing vaccines. In a recent article in the journal *Blood*, Noelle described an experimental cancer vaccine that triggers the innate *and* acquired immune responses, resulting in a vast improvement over treatments that activate only one or the other.

Innate immunity provides the first defense against pathogens, responding almost immediately when a viral or bacterial invader enters the body. This response is prompted by toll-like receptors (TLRs), which are present in several types of cells involved in immunity. When they recognize a pathogen, they bind to bits of it, leading to swelling at the site of the infection and a low fever—signs the body is trying to fight off a threat.

Critical: This initial response is a critical part of fighting disease. "You've got to be able to initiate the immune response within minutes to hours," says Noelle. "You'd be dead without your innate immune system."

Acquired immunity, the next layer of protection, is activated in large part by the receptor CD40. Once stimulated, this molecule fires up an all-out defense against a pathogen. Noelle calls it "the on-off switch for acquired immunity. Without CD40, you don't make antibodies, you don't make cytotoxic T cells, you don't make inflammatory T cells."

Cells: Together, innate and acquired immunity shield humans from a world full of potentially harmful viruses and bacteria. But they often have trouble reacting to tumor cells, because those cells can appear similar to normal human cells, so the immune system doesn't mount a response. Cancer vaccines succeed by mimicking a natural pathogen, causing the immune system to respond to tumor cells that it might otherwise leave alone.

"The magnitude of the immune response… is spectacular," he says.

Noelle's lab has developed a way to stimulate both TLRs and CD40 with a single treatment—with impressive results. "The magnitude of the immune response that you get is spectacular," he says. In experiments with mice, he found that this approach is far more effective than activating either TLRs or CD40 alone.

To conduct the experiment, mice were injected with tumor cells. Then some of the mice were administered a vaccine that triggered only TLRs or CD40, while others were given a vaccine that stimulated both. Noelle found that the average survival time was 30 days for mice given the vaccine that activated TLRs alone, 35 days for those given the vaccine that activated CD40 alone, and 47 days for those given the combination therapy. Just as impressive was the fact that 20% of the mice in the third group survived 90 or more days, compared to only 3% in the CD40-only group and none in the TLR-only group. When Noelle took a closer look at the mice, he found that the combination therapy had induced the production of many more CD8+ T cells, the most effective soldiers in the battle against tumor growth.

The combination therapy also resulted in the creation of more cells involved in the immune system's long-term memory. So if the tumor reappeared after being defeated initially, there was a better chance the mice would be able to fight it off again.

A final benefit of the two-pronged approach is that it mitigated a harmful side effect associated with treatments that trigger CD40 alone. Previous studies in both animal and human models have shown that vaccines that stimulate CD40 can result in liver damage. The fear was that adding another activator would make things worse. "But as it turns out," says Noelle, "it completely ameliorates toxicity." The reasons are not entirely clear, but he thinks the finding shows that "you shouldn't be activating one immune system without the other."

Track: These results have convinced Noelle, who is currently the acting chair of microbiology and immunology, that he's on the right track. "The question," he says, "is whether we can move this into humans."

Drug companies have tested therapies using either CD40 or TLRs, without much success. Noelle hopes to translate his results into a vaccine that can go to clinical trials. He thinks the outcome could be quite an improvement. "Retrospectively," he says, "it's obvious . . . that you've got to activate both of your immune systems." AMOS ESTY