Viral boost for cancer immunotherapies

By Kai-Jye Lou, Staff Writer

Researchers at **Hannover Medical School** and **District Clinics Reutlingen** have used oncolytic viruses to break immune tolerance toward tumor cells and thus boost the efficacy of dendritic cell-based cancer vaccines.¹ The group is now evaluating whether virus-induced tumor inflammation could bolster the efficacy of other classes of cancer immunotherapies.

Immune tolerance toward tumor cells and the low inherent immunogenicity of many tumor-associated antigens make it difficult to stimulate a robust antitumor immune response and can limit the efficacy of cancer immunotherapies.

To help break this tumor-specific immune tolerance, a German group looked to combine a dendritic cell (DC)-based vaccine with one of nature's most potent immune system stimulators—the virus.

“There are few things that the immune system recognizes as more dangerous than a replicating virus,” said David Kirn, founder, president and CEO of oncolytic virus company **Jennerex Inc.**

Viral infections stimulate so-called cellular danger pathways that alert the host immune system to injury, stress and abnormal cell death. Activation of these pathways triggers a strong immune response. Past studies also have shown that viral infections can induce an immune response against antigens that normally wouldn't be presented by DCs.^{2,3}

Thus, the German-led group hypothesized that an oncolytic virus would provide the cellular danger signal to boost the antitumor immune response elicited by a DC vaccine while also revealing additional tumor-associated antigens to the immune system.

The first step was measuring tumor inflammation following injection with an oncolytic virus to determine the best point at which to deliver the DC vaccine.

In mouse models of lung cancer, intratumoral injection of an oncolytic adenovirus resulted in maximum tumor inflammation at day three. At this time point, the combination of oncolytic virus and DC vaccine caused tumor regression, whereas monotherapy with either agent alone only inhibited tumor growth ($p \leq 0.05$).

The DC vaccines were generated by pulsing the cells with tumor lysates. Importantly, the researchers found that the immune response elicited by the combination therapy was specific to the tumor type used

to generate the DC vaccine, confirming that the effect was antigen specific and not the result of general tumor inflammation.

Results were published in *The Journal of Clinical Investigation*.

“Our study shows that having inflamed tumor tissue is an important precondition for generating a strong antitumor immune response with dendritic cell vaccination,” said Stefan Kubicka, co-corresponding author on the paper and director of the Department of Internal Medicine at District Clinics Reutlingen. “When we used dendritic cell vaccination alone or at a time point after virotherapy without tumor inflammation, it resulted in a low number of activated T cells and a weak immune response in the tumor-bearing mice.”

Kubicka said his group previously tried combining DC vaccines with nonreplicating viruses and with nonviral immunostimulatory molecules such as toll-like receptor (TLR) ligands. However, he noted that the resulting antitumor immune responses were not as strong as those produced by combination with the replicating oncolytic adenovirus used in the current study.

“I think the idea is pretty new but follows logically from the increased understanding that viral inflammation can be useful for antitumor vaccination,” said Akseli Hemminki, a research professor and leader of the Cancer Gene Therapy Group at **University of Helsinki**. “DC-based vaccines can suffer from low efficacy in humans, and using an oncolytic virus could help boost activity.”

From mono to combo

“I think the described approach seems like a very logical combination and makes a ton of sense,” said Jennerex's Kirn. “To achieve successful anti-cancer immunity, it's generally not sufficient to

just target an individual cytokine or tumor antigen. What one really needs is an approach that stimulates multiple aspects of anticancer immunity.”

The biotech's lead candidate, JX-594, a recombinant vaccinia virus with a thymidine kinase (TK) deletion and granulocyte macrophage colony-stimulating factor (GM-CSF; CSF2) addition, has completed Phase II testing to treat hepatocellular carcinoma (HCC) and is now entering a Phase IIb trial. The compound also is in Phase I testing for colorectal cancer and for solid tumors.

GM-CSF is an immunostimulatory cytokine that could help confer vaccine-like properties to the oncolytic virus. However, Kubicka's paper marks the first to show that the oncolytic virus itself improves the efficacy of a DC cancer vaccine.

Hemminki, who also is CSO and cofounder of oncolytic virus company **Oncos Therapeutics Ltd.**, said because oncolytic viruses only replicate in tumors, the oncolysis-associated danger signal is restricted to the tumor, which could help decrease systemic exposure.

The recruitment of immune cells to the tumor site and the resulting inflammation also could aid the presentation of many tumor-associated antigens by DCs and other antigen-presenting cells and thus increase the specificity of the resulting antitumor immune response.

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**—Stefan Kubicka,
District Clinics Reutlingen**

“You let the patient’s immune system decide which tumor antigens to best target, so the resulting immune response would be specific for that patient’s tumor,” said Kirn.

Kubicka said the findings in the paper also suggest the possibility of combining the oncolytic viruses with other classes of cancer immunotherapies.

For example, he and Kirn both agree that oncolytic virus therapy could pair well with Yervoy ipilimumab from **Bristol-Myers Squibb Co.** The human mAb against CTLA-4 (CD152) receptor received FDA approval in March to treat unresectable or metastatic melanoma.

CTLA-4 is a negative regulator of T cell activation. Blocking this antigen increases T cell activation and proliferation, which could strengthen a T cell-mediated antitumor immune response. Oncolytic virus-induced tumor inflammation could further augment this response.

Kubicka added that in addition to lung cancer, other solid tumors like colorectal, breast and pancreatic cancers could benefit from the use of oncolytic virus therapy, particularly in the neoadjuvant setting before cancer resection.

Hemminki noted that the ideal patient population for an oncolytic virus plus a DC vaccine combination would have low tumor load, a good performance score and slow-growing tumors.

Clinicians use performance scores to assess disease progression and a patient’s quality of life.

Considerations for combinations

Kirn said that when considering the combination of oncolytic viruses with other immunotherapies, it will be important to determine the optimal level of immunostimulation.

“If you stimulate the immune response too much, it could lead to toxicity or result in the oncolytic virus getting cleared from the body too

quickly,” he told *SciBX*. “For each combination it will also be important to determine the optimal sequence and timing on when to give the oncolytic virus and when to give the other immunotherapy.”

Kirn also wanted to see the findings in the paper duplicated with a different oncolytic virus like vaccinia.

He noted that vaccinia can be efficiently delivered intravenously. He added that vaccinia also replicates and spreads rapidly through the tumor, so it avoids getting cleared too quickly by the host immune system.

Kubicka said his group is now exploring the possibility of replacing the dendritic cell vaccination step with an immunotherapy approach that would not be patient specific.

“Dendritic cell vaccines can only be used in a very individualized setting and are difficult to develop as clinical therapies,” he said.

The work described in the paper is unpatented.

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REFERENCES

1. Woller, N. *et al. J. Clin. Invest.*; published online June 6, 2011; doi:10.1172/JCI45585
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2. Chen, M. *et al. J. Virol.* **79**, 2964–2972 (2005)
3. Schulz, O. *et al. Nature* **433**, 887–892 (2005)

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