Melanoma checkpoint inhibitors

By Lauren Martz, Staff Writer

Immune checkpoint proteins are among the hottest targets in the cancer immunotherapy space, but many patients do not respond to individual antibodies against the targets. A team of U.S. researchers has found that combining a cocktail of antibodies targeting checkpoint proteins with peptide-based cancer vaccines induced a potent and tumor-specific T cell response to treat melanoma.¹

Researchers on the paper founded cancer immunology company **CoStim Pharmaceuticals Inc.** in 2011. The company is developing combinations of undisclosed checkpoint inhibitors.

Immunological checkpoint proteins including CTLA-4 (CD152) and programmed cell death 1 (PDCD1; PD-1; CD279) function as regulatory controls to dampen excessive T cell activation and prevent autoimmunity. In cancer, prolonged activation of the checkpoint proteins leads to T cell exhaustion and senescence, allowing tumors to evade the immune response.

Antibodies against these checkpoint modulators can reactivate T cells, which in turn mount an antitumor response. Yervoy ipilimumab, a human mAb against CTLA-4 from **Bristol-Myers Squibb Co.**, is the first checkpoint inhibitor to reach the market. The antibody was approved to treat metastatic melanoma in 2011.

Bristol-Myers and **Ono Pharmaceutical Co. Ltd.** have the most advanced PD-1 antibody, nivolumab, which is in Phase III testing for metastatic melanoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC).

Because antibodies targeting checkpoint inhibitors are only effective in subsets of patients with melanoma, Bristol-Myers tested a combination of antibodies targeting CTLA-4 and PD-1.

When Yervoy and nivolumab were tested in combination in metastatic melanoma, Bristol-Myers reported that all patients showed at least 80% tumor shrinkage within 12 weeks. In separate trials in a similar patient population, either therapy alone produced the same level of shrinkage in only 2%–3% of patients.

Last year, a **University of Pennsylvania** team found that combining antibodies against PD-1 and CTLA-4 with a cancer vaccine caused more

tumor rejection in mouse models of colon and ovarian cancers than any individual therapy.²

Hassane Zarour and colleagues have now found that cancer vaccines upregulate checkpoint proteins on T cells, which could be responsible for reducing efficacy. The group combined antibodies against PD-1 and another checkpoint target called TIM3 (hepatitis A virus cellular receptor 2; HAVCR2) with peptide-based tumor vaccines.

Zarour is an associate professor of medicine at the **University of Pittsburgh School of Medicine**. The paper also included researchers from **The University of North Carolina at Chapel Hill**, the **University of Lausanne**, **Pfizer Inc.**, **Brigham and Women's Hospital** and **Harvard Medical School**.

The team studied peripheral blood mononuclear cells (PBMCs) isolated from patients with melanoma who were treated with vaccines against major histocompatibility complex class I (MHC) and MHCII cancer/testis antigen 1B (CTAG1B; NY-ESO-1) peptides. PD-1 was upregulated following vaccination in about 73% of CD8⁺ T cells from the patients, and TIM3 was upregulated in about 18% of the cells.

These findings suggest that although tumor vaccines expand antigen-specific T cells in patients, they also upregulate inhibitory receptors on the T cells that prevent their activity.

Indeed, higher levels of PD-1 and TIM3 prior to vaccination correlated with decreased expansion of antigen-specific T cells following immunization.

In PBMCs isolated from eight patients with melanoma after biweekly vaccinations for four months, incubation with the NY-ESO-1 peptide plus antibodies blocking PD-1 or TIM3 increased the number of proliferating and tumor antigen-specific CD8⁺ T cells and the levels of cytokine production by the cells compared with IgG control.

The combination of anti-PD-1 and anti-TIM3 antibodies had an additive effect on

T cell proliferation and cytokine production.

These findings suggest that combining PD-1 and TIM3 blockade with cancer vaccines could stimulate the T cell response and activity of T cells against tumor antigen-expressing cancer cells.

Results were published in *Cancer Research*.

Combination advantages

“One thing that sets this work apart is the finding that suggests blocking one pathway alone is not enough,” noted Gunnar Kaufmann, senior director of R&D at **Sorrento Therapeutics Inc.**

Sorrento has a human programmed cell death 1 ligand 1 (CD274 molecule; PD-L1; B7-H1) mAb in preclinical testing to treat cancers.

Paul Anthony, an assistant professor of microbiology and immunology at the **University of Maryland School of Medicine**, added, “PD-1 and TIM3 are not redundant, meaning each molecule has a separate pathway that exerts a negative signal on T cell function.

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Michael Schickler, CEO of **CureTech Ltd.**, said that there should be more studies to firm up the case for hitting PD-1 and TIM3 together. “We don’t know if PD-1 and TIM3 are the only culprits impeding the T cell response, but this is a nice start,” he said.

CureTech’s pidilizumab, a humanized mAb targeting PD-1, is in Phase II testing for cancers including melanoma.

David King, CSO of **AnaptysBio Inc.**, said that the question of which combinations of checkpoints to inhibit will vary from patient to patient based upon the phenotypic markers expressed by the patient’s tumor.

“You could envision a clinical development strategy that improves therapeutic outcomes by targeting specific patient populations where immune checkpoint inhibition is most

relevant,” said Hamza Suria, president and CEO of AnaptysBio. The company’s ANB011, an anti-PD-1 antibody, is in preclinical testing to treat cancer. The company also is developing a portfolio of antibodies targeting T cell negative regulators including PD-1, TIM3 and lymphocyte-activation gene 3 (LAG3; CD223).

Dixon Gray, senior scientist at Sorrento, agreed. “Modulation of the immune system is highly patient dependent, so it would be hard to have a one-method-fits-all approach here. One should prescreen the patient population for potential responders,” he said.

Kaufmann thinks that based on the reported findings, the researchers could “expand their investigation into a clinical setting and rerun the human study from the paper actually administering the antibodies to the patients. While there was no response to the vaccine regimen in the

trial referenced, a combination with these two antibodies could induce a positive patient antitumor response.”

The patent and licensing status of the combined immunotherapy approach for melanoma is unavailable.

Vijay Kuchroo, a professor of neurology at Harvard Medical School, an associate immunologist at Brigham and Women’s Hospital and an author on the paper, cofounded CoStim.

CoStim said that it is not financially supporting the work published in the *Cancer Research* paper.

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REFERENCES

1. Fourcade, J. *et al. Cancer Res.*; published online Dec. 16, 2013; doi:10.1158/0008-5472.CAN-13-2908
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2. Duraiswamy, J. *et al. Cancer Res.* **73**, 3591–3603 (2013)

COMPANIES AND INSTITUTIONS MENTIONED

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