N-Cadherin block against prostate cancer

By Kai-Jye Lou, Staff Writer

University of California, Los Angeles researchers have shown that mAbs targeting the cell surface protein N-cadherin can inhibit prostate cancer growth, metastasis and progression to castration-resistant disease.¹ If **Emtx Therapeutics Inc.** exercises its option to license and develop N-cadherin-specific antibodies for use in cancer, it could have a candidate ready for clinical testing in two to three years.

Although androgen ablation is one of the mainstays for treating prostate cancer, many patients still progress to castration-resistant disease in 12–18 months.² Nearly all pathways that are associated with the transition from androgen-dependent to castration-resistant disease include reactivation of signaling pathways that involve the androgen receptor (AR).^{3,4}

Although there are at least three second-generation therapies in the clinic that can block AR signaling in castration-resistant tumors, some patients are still nonresponsive or only partially responsive to the molecules. Those findings suggest that castration-resistant prostate cancer (CRPC) can become partially or completely independent of AR signaling.

Previous studies have associated N-cadherin expression with high-grade prostate cancer and metastasis,^{5–7} although the effects of inhibiting the cell surface protein and its precise contribution to castration-resistant disease were never explored.

Now, a UCLA group led by Robert Reiter has identified an N-cadherin-mediated pathway that could promote independence from AR signaling and progression to CRPC.

Reiter is a professor of urology at UCLA and founder of Emtx Therapeutics, a biotech startup that has an option to license the new findings.

His group found progressively higher levels of N-cadherin expression in tumor samples from patients who had not received androgen ablation therapy, those who received such therapies and those who developed CRPC.

In mice with AR⁺ or AR⁻ human prostate cancer, mAbs against the extracellular domain of N-cadherin inhibited tumor growth and metastasis. The therapeutics also delayed the development of castration-resistant disease compared with vehicle.

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—Robert Reiter,
University of California,
Los Angeles

Results were published in *Nature Medicine*.

“Our work validates N-cadherin as a target for prostate cancer therapy and may also explain one of the significant pathways by which prostate tumors become castration resistant,” said Reiter, who is the corresponding author on the paper. “We also found that in prostate cancer cells, increased N-cadherin expression leads to reduced androgen receptor expression, which suggests that an antibody against N-cadherin could synergize with androgen receptor-targeting therapies or reduce resistance against them.”

“If N-cadherin expression leads to loss of androgen receptor expression, and if that is shown to play a role in the development of tumor resistance to androgen receptor blockers, it is possible that inhibition of N-cadherin, in addition to inhibiting a possibly important new avenue of tumor resistance, might actually resensitize tumors to androgen receptor-targeted therapies,” said David Hung, president and CEO of **Medivation Inc.**

However, he added, “we will need to know if such a combination would be tolerable. We know from our own clinical trials that MDV3100 is quite well tolerated, with the most significant side effect being fatigue, but the safety profile from targeting N-cadherin therapy is not known.”

In September, Medivation and partner **Astellas Pharma Inc.** began a second Phase III trial of MDV3100 in patients with metastatic prostate cancer who are progressing despite treatment with androgen deprivation therapy. Medivation is also evaluating the triple-acting, oral antiandrogen in a Phase III trial that has completed enrollment of patients with CRPC previously treated with chemotherapy.

Reiter agreed that additional studies need to flesh out the safety profile of an N-cadherin-targeting therapy, as the cell surface protein is broadly expressed in multiple normal tissues. He did say there was no evidence of toxicity in mice treated with the mAbs in the *Nature Medicine* study.

Beatrice Knudsen, an associate professor at the **Fred Hutchinson Cancer Research Center**, noted that the lack of toxicity in the mouse studies suggests N-cadherin has different activity in malignant and normal cells.

“The signaling pathways in cancer cells may be different from that of normal cells such that blocking N-cadherin is lethal to the former but not to the latter,” she told *SciBX*.

Depending on how the toxicity studies pan out, Hung thinks that an N-cadherin-targeting compound also could have utility in the second-line setting or as salvage therapy for patients whose disease is advancing despite treatment with standard therapies.

“Right now, patients that have end-stage prostate cancer have very few treatment options, and while chemotherapy is a possibility, it is obviously very toxic and not well tolerated,” he told *SciBX*. “An N-cadherin-targeting therapy could be better tolerated than chemotherapy and thus provide an alternative.”

Pathways to development

In addition to safety, both Hung and Knudsen wanted to know the extent of N-cadherin's involvement in prostate cancer.

"We know that androgen receptor signaling is important in the majority of prostate cancers, but what we don't yet know is the prevalence of N-cadherin-mediated tumor growth," said Hung. "It will be important to determine how prevalent the N-cadherin pathway is in prostate cancer and whether it is redundant or independent and unrelated to other pathways that are already being targeted."

"I think these preclinical data show a lot of promise for prostate cancers that express N-cadherin," said Knudsen. "In the future, it will be important to determine the threshold of N-cadherin expression needed for a targeted therapy to be effective and to determine how widely N-cadherin is expressed."

She also wanted to see studies that assess the likelihood of cancer cells developing resistance to an N-cadherin-targeting therapy.

Reiter said his group is trying to elucidate the mechanisms by which N-cadherin confers castration resistance and how it may contribute to decreased AR expression to help guide development of rational combinations with existing prostate cancer therapeutics, like the AR antagonists. The group also is optimizing the N-cadherin-targeting mAbs for human use.

Reiter said that if the group decides to proceed with commercialization through Emtx, a candidate could be moved into the clinic within two to three years.

UCLA has filed multiple patent applications covering the work.

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COMPANIES AND INSTITUTIONS MENTIONED

Astellas Pharma Inc. (Tokyo:4503), Tokyo, Japan

Emtx Therapeutics Inc., Los Angeles, Calif.

Fred Hutchinson Cancer Research Center, Seattle, Wash.

Medivation Inc. (NASDAQ:MDVN), San Francisco, Calif.

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