Personalizing the prostate

By Chris Cain, Staff Writer

Although the epidermal growth factor receptor is overexpressed in prostate cancer, efforts to repurpose inhibitors that are marketed for other solid tumors have met with little success. Now, researchers at the **University of Michigan Medical School** think they have found a marker for prostate cancers that are susceptible to inhibitors of the receptor—a secreted protein called SPINK1 that is structurally related to epidermal growth factor.

In 2008, a team led by Arul Chinnaiyan, professor of pathology at the medical school, first showed that high levels of serine peptidase inhibitor Kazal type 1 (SPINK1), which occurs in about 10% of patients with prostate cancer, were correlated with a greater rate of cancer recurrence.¹

Additional *in vitro* experiments in SPINK1⁺ prostate cancer cells showed that small interfering RNA knockdown of the target decreased invasiveness. In 2010 a Finnish group at the **University of Tampere** confirmed the finding in an independent population.²

“Two independent studies across multiple independent cohorts have validated this as a target in a subtype of prostate cancer,” said Chinnaiyan. “The result is very clear: you are either SPINK1 positive or negative—it is black or white.”

Thus, Chinnaiyan’s team began a study to determine the therapeutic effect of targeting SPINK1 in mouse models of prostate cancer.

The team published *in vivo* data this month that confirmed SPINK1’s potential as a therapeutic target but also revealed a surprising twist—SPINK1 promoted prostate tumor growth in part by signaling through the epidermal growth factor receptor (EGFR).³

Indeed, the anti-EGFR mAb Erbitux cetuximab decreased tumor growth in mice with SPINK1⁺ tumors but had no effect on SPINK1[−] tumors.

Co-injection of anti-SPINK1 and anti-EGFR mAbs reduced tumor growth more than injection of either agent alone, suggesting that SPINK1 has both EGFR-dependent and EGFR-independent roles in promoting prostate tumor growth.

Results were published in *Science Translational Medicine*.

Rethinking EGFR

The findings suggest that it might be worthwhile to revisit the

potential of EGFR inhibitors in prostate cancer, which thus far have not shown compelling results.⁴

For example, only 3 of 36 patients with metastatic, castration-resistant prostate cancer showed >50% decline in prostate-specific antigen (KLK3; PSA) levels in a Phase Ib/IIa trial of Erbitux plus doxorubicin.⁵ Two additional Phase II trials of the small molecule EGFR inhibitors Tarceva erlotinib and Iressa gefitinib also showed minimal benefits.^{6,7}

Chinnaiyan is now collaborating with Susan Slovin, associate attending physician at **Memorial Sloan-Kettering Cancer Center**, who ran the trial of Erbitux in prostate cancer patients. They plan to retrospectively analyze the SPINK1 levels of patient tissue samples to determine if SPINK1 expression is predictive of Erbitux response.

Chinnaiyan also is collaborating with Christopher Logothetis, chair of the Department of Genitourinary Medical Oncology at **The University of Texas M.D. Anderson Cancer Center**, to test SPINK1 inhibition

in mice with prostate cancer cells directly taken from SPINK1⁺ human tumors.

“One of the issues with prostate cancers in general is that there are too few cell lines. We were lucky that one of the cell lines commonly used in prostate cancer happened to be SPINK1⁺; most of the other commonly used cell lines are not,” said Chinnaiyan.

Two SPINK1⁺ cell lines have been tested so far, both independently derived from the same patient.

Chinnaiyan also plans to continue developing antibodies against SPINK1. “To take this finding to the next level, we are developing a panel of SPINK1 monoclonal antibodies and will test the efficacy of these antibodies more rigorously in a single- or combination-treatment regimen in our SPINK1 preclinical models,” he said.

“Given the aggressive nature of castration-resistant prostate cancer, including a SPINK1 inhibitor should be highly feasible in a Phase I or II clinical trial,” said Mark Rubin, vice chair of experimental pathology at **Weill Cornell Medical College**. “These could immediately address how well the drugs are tolerated and if there is any decrease in the tumor burden.”

Rubin previously collaborated with Chinnaiyan to identify SPINK1 expression as a marker of prostate cancer progression. Rubin was not involved with the new paper.

Chinnaiyan said the University of Michigan has filed a patent for SPINK1 as a biomarker of prostate cancer and as a therapeutic target. **Gen-Probe Inc.** has licensed the diagnostic field of use but did not respond to requests for comment on its development. The therapeutic field of use is available for licensing, and Chinnaiyan said the university is in talks with potential industry partners.

He added that his lab is not in a position to generate humanized mAbs that could be used outside of preclinical models but said it is set up to test and characterize humanized antibodies that a partner could create.

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—Mark Rubin,
Weill Cornell Medical College

Erbix is marketed to treat metastatic colorectal cancer (mCRC) and squamous cell carcinoma of the head and neck (SCCHN) by the **ImClone Systems Inc.** subsidiary of **Eli Lilly and Co.** and **Bristol-Myers Squibb Co.** in North America. **Merck KGaA** markets the drug elsewhere, except in Japan, where the three companies market the drug.

Tarceva is marketed by **Astellas Pharma Inc.**'s **OSI Pharmaceuticals Inc.** subsidiary and **Roche's Genentech Inc.** unit for non-small cell lung cancer (NSCLC) and pancreatic cancer. **AstraZeneca plc** markets Iressa for NSCLC outside the U.S.

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COMPANIES AND INSTITUTIONS MENTIONED

Astellas Pharma Inc. (Tokyo:4503), Tokyo, Japan
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Bristol-Myers Squibb Co. (NYSE:BMJ), New York, N.Y.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Genentech Inc., South San Francisco, Calif.
Gen-Probe Inc. (NASDAQ:GPRO), San Diego, Calif.
ImClone Systems Inc., New York, N.Y.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
Merck KGaA (Xetra:MRK), Darmstadt, Germany
OSI Pharmaceuticals Inc., Melville, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
University of Michigan Medical School, Ann Arbor, Mich.
University of Tampere, Tampere, Finland
The University of Texas M.D. Anderson Cancer Center, Houston, Texas
Weill Cornell Medical College, New York, N.Y.