Paclitaxel: wrong foot forward in cancer?

By Michael J. Haas, Senior Writer

In vitro studies by researchers from the **Sanford-Burnham Medical Research Institute** and the **University of California, San Diego** suggest that the generic chemotherapeutic paclitaxel increases metastasis in some cancers by promoting the formation of invadopodia—foot-like cell membrane protrusions that enable primary tumor cells to become invasive.¹ The team also showed *in vitro* that cyclin dependent kinase 5 inhibitors blocked invadopodia formation—including that induced by paclitaxel.

The next step is *in vivo* studies to investigate the relevance of the findings to paclitaxel-treated cancers.

Over the past two decades, multiple studies have linked invadopodia on tumor cells with the degradation of the extracellular matrix (ECM) and a concomitant increase in tumor cell invasion and metastasis. To better understand the mechanisms underlying invadopodia formation, the team screened a library of 1,280 small molecules to identify inhibitors and activators of the process.

Because unmodified cancer cell lines do not reliably produce large numbers of invadopodia, the team first screened the compound library in src-expressing mouse embryonic fibroblasts—a cellular model capable of invadopodia formation.^{2,3} The initial screen identified 20 potential inhibitors and 8 activators of invadopodia formation.

Next, the team validated the 28 hits in a matrix-degradation assay that modeled the invasive activity of multiple cancer cells—including head and neck carcinoma, non-small cell lung cancer (NSCLC), ovarian cancer and melanoma.

The assay confirmed five hits as inhibitors of invadopodia formation: two src inhibitors, one MEK inhibitor that the team identified in a previous study⁴ and two compounds—including purvalanol A—that were already known to inhibit multiple cyclin dependent kinases (CDKs). The team went on to show that the two new hits blocked invadopodia *in vitro* by inhibiting cyclin dependent kinase 5 (CDK5).

The assay also confirmed that two compounds—paclitaxel and the terpenoid toxin cantharidin—activated invadopodia formation.

Lastly, the team showed that in a human ovarian cell line resistant to paclitaxel-induced apoptosis, paclitaxel increased invadopodia

formation compared with vehicle, whereas the drug plus purvalanol A blocked invadopodia formation.

In its report in *Science Signaling*, the team noted that results from three studies by other research groups suggested paclitaxel might play a role in tumor cell invasion and metastasis. Two of those studies showed increased metastases in mice with paclitaxel-resistant leukemia⁵ and paclitaxel-resistant ovarian xenografts.⁶ The third showed that in breast cancer patients receiving paclitaxel, levels of circulating epithelial tumor cells were more than 1,000-fold higher than pretreatment baselines,⁷ suggesting the drug increased tumor cell mobility and extravasation.

Taken together, those previous studies and the team's own findings “hint that paclitaxel-induced metastasis might be occurring in patients who are refractory or nonresponsive to paclitaxel” and possibly other taxane chemotherapies, team coleader Sara Courtneidge told *SciBX*.

But she acknowledged that it was not yet clear whether or how frequently paclitaxel promoted metastasis in patients. Therefore, “It will be important to establish whether our *in vitro* results are relevant *in vivo*,” she said.

Courtneidge is a professor and director of the Tumor Microenvironment Program and director of academic affairs at Sanford-Burnham. She co-led the team with Manuela Quintavalle, a postdoctoral researcher in her group. The team included a scientist from UCSD.

Lance Leopold, CMO and VP of clinical development at **Ascenta Therapeutics Inc.**, agreed that establishing the clinical relevance of the team's findings will be key, because numerous clinical trials have shown the benefit of taxanes in many tumor types.

“Whether there is a subset of patients that is made worse by this class of agents remains a speculative but interesting question,” he said.

“The answer could be important for all tumor types where taxanes are used,” including NSCLC, and breast, head and neck, ovarian and gastric cancers.

“The potential relevance of these findings could be quite ranging,” said Paul Workman, deputy CEO and director of the **Cancer Research UK Cancer Therapeutics Unit** at **The Institute of Cancer Research**. “It will be important to consider the potential for very serious adverse events against the well-established therapeutic activity of the drug” by studying it in various mouse models of cancer invasion and metastasis, he said.

He also wanted to see studies exploring the genetic subtypes of different cancers that might be especially susceptible to the adverse effects of paclitaxel.

Indeed, Courtneidge said her team is now investigating whether paclitaxel and CDK5 inhibitors have pro- and antimetastatic effects, respectively, in mouse models of cancer.

She said those *in vivo* studies include testing whether paclitaxel

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**—Lance Leopold,
Ascenta Therapeutics Inc.**

is prometastatic in neoadjuvant settings, in which drug treatment is usually expected to shrink tumors and make them more amenable to surgical resection.

“Neoadjuvant use of paclitaxel is more concerning to us than its use in other situations because the primary tumor is still in place, and you don’t want to do anything to increase the risk of the cancer cells becoming invasive or metastasizing,” she said. After surgery, that risk is hypothetically lower, but the hypothesis “needs to be examined in animal models before we can conclude that is the case.”

She added that the **Foundation for the National Institutes of Health** has paclitaxel in Phase II testing as a neoadjuvant to treat breast cancer. “While the potential danger paclitaxel poses in any treatment setting has yet to be shown—in animal models or in humans—we hope that our study will at least open a discussion about the possibly negative consequences of neoadjuvant therapies,” she said.

But she pointed out her team showed that CDK5 inhibition reversed paclitaxel’s invadopodia-promoting effect—thus suggesting the chemotherapy could still help kill primary tumors if coadministered with an invadopodia inhibitor.

Workman agreed. Although suggesting the potential need for caution in the clinical use of paclitaxel, “these studies also open up the exciting possibility of combining paclitaxel with agents that inhibit CDK5 to block the increase in invadopodia and thus prevent the

stimulation of invasion and metastasis,” he said.

Courtneidge said her team is conducting additional screens to identify other targets involved in invadopodia formation and thereby broaden the range of potential inhibitors.

The findings in *Science Signaling* are unpatented and available for licensing or partnering, she said.

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COMPANIES AND INSTITUTIONS MENTIONED

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