A new boost from sildenafil

By Steve Edelson, Executive Editor

Pfizer Inc.'s vasodilator sildenafil, marketed as Viagra for erectile dysfunction and as Revatio to treat pulmonary arterial hypertension, also could have utility in oncology, according to new findings by researchers at **Virginia Commonwealth University**. The team found that sildenafil has a unique synergy with doxorubicin: it not only reduces the chemotherapeutic's cardiotoxicity but also potentiates its efficacy.¹

Doxorubicin is widely used in a host of cancers, but the drug's label includes a boxed warning of myocardial toxicity, including potentially fatal congestive heart failure (CHF).

The VCU team first found hints that sildenafil, a phosphodiesterase-5 (PDE-5) inhibitor, could work well with doxorubicin in 2005. That year, the researchers reported that PDE-5 inhibitors protected mice from doxorubicin-induced cardiotoxicity.²

"One of the major side effects of doxorubicin is irreversible heart damage, and after several years treatment actually has to stop," noted Anindita Das, an assistant professor of internal medicine at VCU. "We wanted to prevent this side effect or protect the heart."

With clear suggestions of a safety advantage for sildenafil plus doxorubicin, a key outstanding question was whether the combination also would yield better efficacy than doxorubicin alone.

In a paper published in the *Proceedings of the National Academy of Sciences*, the VCU researchers reported that in mice with prostate cancer xenografts, sildenafil plus doxorubicin significantly inhibited tumor growth compared with either agent alone.

The combination also substantially increased tumor cell apoptosis compared with monotherapy using sildenafil or doxorubicin. The group generated similar results in mouse models of ovarian cancer and sarcoma.

Finally, the group confirmed its previous findings that sildenafil decreased the cardiotoxicity of doxorubicin in mice.

Elusive mechanism

The mechanism by which sildenafil improves the safety and efficacy of doxorubicin remains elusive. Das, who was lead author of the *PNAS* paper, noted that the team had not been able to replicate the PDE-5 inhibitor's effects with any other chemotherapeutic.

She suspects the Pfizer drug is exerting its synergistic effects with doxorubicin through multiple mechanisms. For stunting tumor growth, she thinks sildenafil increases reactive oxygen species (ROS) in the mitochondria. Indeed, doxorubicin's main route to killing tumors is via generation of mitochondrial ROS.

Das told *SciBX* that the cardioprotective effects of sildenafil likely come from increasing the expression of nitric oxide synthase, an enzyme that catalyzes the production of nitric oxide (NO), a signaling molecule that helps ameliorate the effects of ischemia and reperfusion injury.

Indeed, the initial efforts to develop the PDE-5 inhibitor focused on angina.

Although the authors of the *PNAS* paper wrote that "exactly how sildenafil sensitizes cancer cells to amplify [doxorubicin]-mediated ROS generation is not clear..." the VCU team already has started a clinical trial of the Pfizer drug plus doxorubicin. The study is enrolling patients with breast and ovarian cancer.

Das said the study is not enrolling prostate cancer patients because doxorubicin is not widely used in clinical practice in that indication.

She also said her team is seeking to uncover "the particular mechanism behind the enhanced cell killing and the reductions in tumor volume that sildenafil produces in conjunction with doxorubicin."

"The doxorubicin findings are really compelling," said Paul Sweetnam, CSO of **Surface**

Logix Inc. The company's SLx-2101 small molecule PDE-5 inhibitor has completed Phase IIa testing in multiple indications, including hypertension, Raynaud's disease and erectile dysfunction.

Surface Logix also is interested in PDE-5's role in cancer, but instead of combining SLx-2101 with a chemotherapeutic, the company has a research collaboration with the **Dana-Farber Cancer Institute** to test SLx-2101 with a targeted cancer drug—**Roche's** anti-VEGF antibody Avastin bevacizumab.

"A lot of cancer patients are taken off Avastin because they become extremely hypertensive," noted Sweetnam. "At Dana-Farber, they've looked through their data and what they seem to believe is that patients who responded well to Avastin were the ones with the most hypertension. So they'd like to keep dosing, which brings it back to PDE-5."

The hypothesis, he said, is that Avastin interferes with levels of cyclic GMP and NO, which are downstream of PDE-5. "Decreased nitric oxide levels cause the vasculature to fall apart. A traditional hypertension drug won't address that but a PDE-5 inhibitor would. And SLx-2101 is the only PDE-5 inhibitor that's specifically designed to have an impact on higher cardiovascular structure and function."

According to Das, VCU plans to seek IP protection for the use of sildenafil with doxorubicin to enhance the chemotherapy.

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Surface Logix Inc.

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COMPANIES AND INSTITUTIONS MENTIONED

Dana-Farber Cancer Institute, Boston, Mass.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Surface Logix Inc., Brighton, Mass.
Virginia Commonwealth University, Richmond, Va.