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KIDNEY CANCER

CRM1—a novel drug target for renal cell carcinoma?

Selective inhibitors of chromosome region maintenance protein 1 (CRM1) might provide therapeutic benefit for patients with renal cell carcinoma (RCC), according to a study published in the *Journal of Urology*. CRM1 is responsible for transporting proteins that contain a nuclear export sequence—which includes the tumour suppressors p53 and p21—from the nucleus into the cytosol.

Researchers led by Robert Weiss at the University of California, Davis, have worked on the role of p21 in RCC for over a decade, contributing to our current understanding that p21 must be localized in the nucleus in order to perform its tumour suppressor functions and that the presence of p21 in the cytosol indicates poor prognosis in patients with RCC. "In light of our work on p21, we decided to evaluate the potential role of CRM1 inhibitors in this disease," explains Weiss.

Here, Weiss and colleagues demonstrate that the CRM1 inhibitors KPT-185 and KPT-251 can inhibit tumour growth *in vitro* and *in vivo*. The cytotoxicity of KPT-185 was found to be higher than that of sorafenib in a number of RCC cell lines, although sorafenib was more toxic to 'normal' renal epithelial cell line NHK, which the authors suggest might reflect its adverse effect profile.

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In vivo, CRM1 inhibition with KPT-251 in a mouse xenograft model was associated with a higher rate of tumour shrinkage than sorafenib treatment ($P = 0.007$). Moreover, animals that received sorafenib had skin abnormalities similar to those experienced by patients, whereas KPT-251-treated mice showed no adverse effects—further evidence to suggest a potential clinical advantage for these inhibitors over sorafenib.

Cell culture experiments confirmed that CRM1 inhibition causes enhanced nuclear localization of p21 and p53 associated with increased apoptosis and cell cycle arrest, all of which presumably contribute to the inhibition of tumour growth.

New pharmacological targets for RCC are certainly welcome. Affected patients often present with metastatic disease, and despite the new generation of targeted therapies that have been approved over the last few years, progression-free survival for these patients is still short, at only 1–2 years. "We plan to move this class of compounds into Phase II clinical trials in RCC," says Weiss. "We are hopeful that this will lead to a novel approach to treatment of human kidney cancer, both at early and late stages."

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Original article Inoue, H. *et al.* CRM1 blockade by Selective Inhibitors of Nuclear Export (SINE) attenuates kidney cancer growth. *J. Urol.* doi:10.1016/j.juro.2012.10.018