PROSTATE CANCER

Ex vivo efficacy of heat shock protein 90 inhibitors

A study using *ex vivo* human prostate tumour explants has provided evidence to suggest that heat shock protein 90 (Hsp90) is a potential treatment target for prostate cancer and suggests that explants should be more widely used in preclinical trials.

Hsp90 folds and stabilizes other (client) proteins—including oncoproteins—into their active conformation and is overexpressed in prostate cancer cells. Inhibition of Hsp90 could, therefore, target a number of oncogenic pathways to retard cancer progression. Previous studies using the Hsp90 inhibitor 17-AAG showed no clinical efficacy in phase II trials, despite promising preclinical data.

The study, published in *Clinical Cancer Research*, compared the therapeutic potential of two Hsp90 inhibitors—AUY922 and HSP990—with 17-AAG in prostate cancer cells *in vitro* and in cultured human prostate tumours.

In vitro studies using LNCaP, VCaP and PC3 cell lines showed that AUY922 and HSP990 dose-dependently inhibited cell proliferation, caused cell cycle arrest and induced cell death, although AUY922 was the more potent of the two compounds. By contrast, 17-AAG inhibited proliferation but had no effect on cell death or cell cycle arrest.

Prostate tumour explants were then used to investigate whether the three Hsp90 inhibitors could induce Hsp70 and decrease Hsp90 client protein levels *ex vivo*. All three compounds induced

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Hsp70 compared with control, but only AUY922 and HSP990 displayed antiproliferative and proapoptotic activity in the explants.

The results as a whole suggest that AUY922 and HSP990 are potent anticancer agents, but that Hsp70 induction is not a useful marker of Hsp90 inhibition, as previously thought. Furthermore it seems likely that if 17-AAG had been tested using this system, it would not have progressed to phase II trials in humans.

“Prostate cancer tissues cultured *ex vivo* can provide clinically relevant information

about therapeutic agents that was not previously achieved using cell lines or animal models,” explains Lisa Butler, who led the study.

Such explant systems could be more widely used to prioritize drugs for clinical trials based on their effect on live human tissues.

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Original article Centenera, M. M. *et al.* Evidence for efficacy of new Hsp90 inhibitors revealed by *ex vivo* culture of human prostate tumors. *Clin. Cancer Res.* doi:10.1158/1078-0432.CCR-12-0782