Hopes that new substance will induce cancer cell suicide

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(Medical Xpress)—The p53 gene plays a key role in the prevention of cancer, by blocking cell growth and triggering programmed cell death or apoptosis. If, however, p53 has mutated and become defective, the cancer cells can acquire the ability to evade apoptosis and become more resistant to therapy. Researchers at Karolinska Institutet and Karolinska University Hospital have now obtained results from the first tests using a new substance that can restore the function of defective p53 and activate apoptosis in cancer cells.

The substance is known as APR-246 and has now been tested on humans in a phase I/II study, which was conducted on 22 patients with advanced blood or prostate cancer. Some of the patients came from the Haematology Centre at the Karolinska University Hospital in, Stockholm, where the study's lead investigator, consultant Dr Sören Lehmann is based. The remainder of the patients were from other clinics in Gothenburg, Lund, Uppsala and Örebro.

The patients received daily infusions of APR-246 for four days. When the researchers analyzed the cancer cells taken before and after treatment, they saw indications that the p53 gene had been activated to varying degrees, and that this had triggered the suicide program in the cancer cells. Ten patients could be evaluated as regards the development of their cancer, and in two of them there were signs of tumour regression.

However, the study was actually not designed to test the clinical effects

but to ascertain how well the substance was tolerated by the body. With the main adverse reactions confined to temporary tiredness, nausea, headache and confusion, their results would suggest that the substance is well tolerated.

"The side-effects were totally different to those produced by conventional chemotherapy, which bodes well for designing combination therapies," says Dr Lehmann. "And it's in precisely this kind of combination that we think the substance has the greatest potential. In previous laboratory studies we've seen that APR-246 has generated synergy gains when used with chemotherapy due to the mutually enhancing effects of both substances."

Defective p53 is considered one of the most common factors behind the development of cancer. In some cancers, such as ovarian cancer, the vast majority of tumours have defective p53. In total, the p53 tumour suppressor gene is mutated in at least half of all tumours.

"In theory, a drug that restores p53 function should be effective against many different kinds of cancer, provided that the individual tumour contains defective p53," says study team member Professor Klas Wiman. "We should keep in mind, however, that tumours are very complex."

More information: Sören Lehmann, et al. Targeting p53 in vivo: A first-in-man study with the p53-targeting compound APR-246 (PRIMA-1MET) in refractory hematological malignancies and prostate cancer. *Journal of Clinical Oncology*, early online publication 10 September 2012, doi: 10.1200/JCO.2011.40.7783.

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