Dual gene therapy shows promising results in preclinical tests

Lung cancer is notoriously difficult to treat but a novel tumor-suppressor gene has been identified that could suppress human non-small cell lung cancer (NSCLC) when used in combination with gene transfer of tumor-suppressor gene *p53*.

Lung cancer is the most common cancer in the world, with 1.3 million new cases diagnosed every year. Almost half of all patients diagnosed with non-small cell lung cancer already have Stage IV disease and lung cancer has one of the lowest survival outcomes of any cancer.

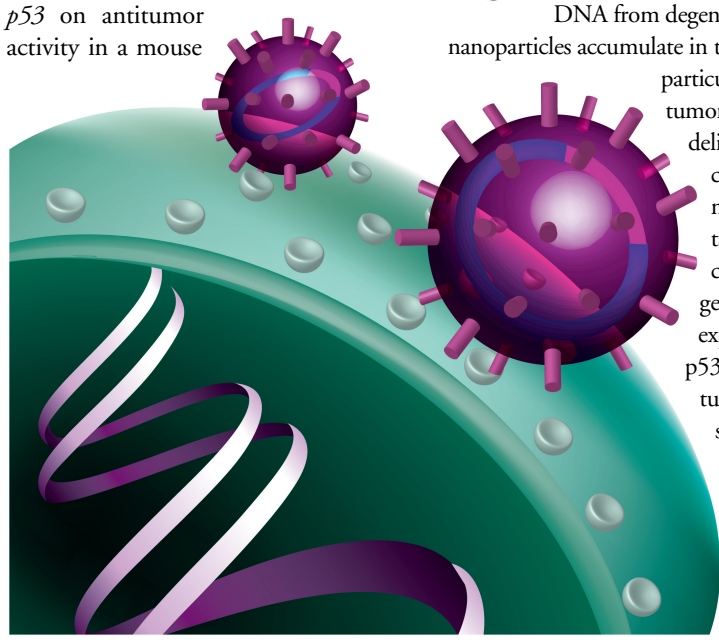
Current treatment options for patients with NSCLC are limited, as only a fifth of patients are considered suitable for surgery; other treatments, such as chemotherapy and radiotherapy, to treat the disease are toxic and dangerous.

> "We certainly hope this approach will be more effective but we also think it's likely to be much less toxic, with fewer side effects, than other types of combined cancer therapy."

The researchers evaluated the combined effects of *FUS1* and *p53* on antitumor activity in a mouse model of human NSCLC. Jack Roth, who led the research, explained why this combination therapy may prove to be effective, "In cancer treatment we have combination chemotherapy, and we also combine different modes of therapy – surgery, radiation and chemotherapy. Now you've got the possibility of combined targeted gene therapy."

"We certainly hope this approach will be more effective but we also think it's likely to be much less toxic, with fewer side effects, than other types of combined cancer therapy." he added.

The two genes were already known to have tumor-suppression properties. *Fus1* is deficient in the majority of human lung cancers and *p53* is well known for its antitumor activity in cancers. The genes were delivered intravenously, using a delivery system consisting of a plasmid gene loaded with *p53* or *Fus1* DNA. The plasmid is wrapped in *N*-[1-(2,3-dioleoyloxyl)propyl]-*N*,*N*,*N*-trimethylammoniummethyl sulfate, a cholesterol nanoparticle, to protect the DNA from degeneration. The nanoparticles accumulate in the lungs, particularly in the tumors, and are delivered to the cancer cell membrane and taken into the cell, where the genes are able to express either p53 or Fus1 tumor-suppressing proteins.



The research initially used *in vivo* cell lines but was later transferred to mice models, where the therapy was shown to synergistically suppress the development and growth of tumors in a human H322 lung cancer orthotropic mouse model.

The dual gene delivery reduced the number of tumors per mouse by 75–80% and the weight of tumors by 80% within 48h of treatment after treatment, leaving the control group unaffected. This huge reduction is thought to be due to the synergistic manner in which the two genes work. The *Fus1* gene is responsible for the downregulation of murine double minute-2 (*MDM2*) expression, which inhibits *p53*. The downregulation of *MDM2* leads to stabilization and accumulation of p53 protein as well as the activation of apoptotic protease-activating factor (Apaf)-1-dependent pathway – a cell-suicide pathway based in the cells' mitochondria.

The genes appear to have little effect on normal noncancerous tissue cells and specifically attack only cancer cells.

These results provide new insights into the molecular mechanism of *Fus1*-mediated tumor-suppression activity and give hope for the development of new gene therapies in cancer treatment. Clinical trials are already in progress to evaluate the safety of the *Fus1* nanoparticles in patients with advanced non-small cell lung cancer. The Phase I trials are for patients who have previously had chemotherapy and are in the late stages of the disease, with the aim of establishing effective and safe doses of the *Fus1* gene so it can be used in combination therapy.

Source: Jayachandran G, Xu K, Minna JD *et al.*: Synergistic tumor suppression by coexpression of FUS1 and p53 is associated with down-regulation of murine double minute-2 and activation of the apoptotic protease-activating factor 1-dependent apoptotic pathway in human non-small cell lung cancer cells. *Cancer Res.* 67(2), 709–717 (2007).